The epidemiology of alcohol consumption across the life course

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MPH

Submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy (Medical Research)

Menzies Research Institute Tasmania

University of Tasmania

November 2018

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Declaration of originality

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The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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Statement of authorship

This thesis includes three papers, in which Duc Hong Du (DD) is not the sole author. DD took the lead in this research. He designed the studies, performed analyses, interpreted the findings and prepared the manuscripts, with contributions from the co-authors. The contributions of each of the authors are detailed as follows.

The paper presented in Chapter 3

Du D, Bruno R, Dwyer T, Venn A, Gall S: Associations between alcohol consumption and cardio-metabolic risk factors in young adults. *Eur J Prev Cardiol* 2017, 24:1967-1978.

The contributions of each author are as follows:

- DD contributed 70% to the study concept and design, performed data analyses, interpreted the findings, literature review, composed the drafts of the manuscript and coordinated revisions of the manuscript.
- RB contributed to the interpretation of the findings and critically revised the manuscript.
- TD contributed to the design of the study, acquisition of data and critically revised the manuscript.
- AV contributed to the design of the study, acquisition of data and critically revised the manuscript.
- SG contributed to the study concept and design, acquisition of data, the interpretation of the findings, and critically revised the manuscript.

The paper presented in Chapter 4

Du D, Bruno R, Blizzard L, Dwyer T, Venn A, Gall S: Patterns of alcohol consumption, carotid intima-media thickness and insulin resistance in young adults. Draft manuscripts completed.

The contributions of each author are as follows:

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- RB contributed to the interpretation of the findings and critically revised the manuscript.
- LB contributed to the interpretation of the findings and critically revised the manuscript.
- TD contributed to the design of the study, acquisition of data and critically revised the manuscript.
- AV contributed to the design of the study, acquisition of data and critically revised the manuscript.
- SG contributed to the study concept and design, acquisition of data, the interpretation of the findings, and critically revised the manuscript.

The paper presented in Chapter 5

Du D, Bruno R, Blizzard L, Dwyer T, Smith JK, Magnussen CG, Venn A, Gall S: The metabolomics signatures of alcohol consumption in young adults. Submitted to *Int J Cardiol* 2018.

The contributions of each author are as follows:

- DD contributed 70% to the study concept and design, performed data analyses, interpreted the findings, literature review, composed the drafts of the manuscript and coordinated revisions of the manuscript.
- RB contributed to the interpretation of the findings and critically revised the manuscript.

- LB contributed to the interpretation of the findings and critically revised the manuscript.
- TD contributed to the design of the study, acquisition of data and critically revised the manuscript.
- KJS contributed to the design of the study and critically revised the manuscript.
- CGM contributed to the design of the study and critically revised the manuscript.
- AV contributed to the design of the study, acquisition of data and critically revised the manuscript.
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Abstract

Background: Understanding the epidemiology of alcohol consumption across the life course is important for better estimating the associations between alcohol and diseases. There is a need for more studies of how alcohol consumption, including alcohol use disorders, evolves over time and the factors influencing any changes.

Aims: This thesis aimed to address novel aspects of the epidemiology of alcohol consumption and related health effects across the life course.

Methods: Data were from a large population-based cohort study, the Childhood Determinants of Adult Health (CDAH) study. Around 2,500 Australians aged 7–15 years in 1985, aged 26–36 years in 2004–06 and aged 31-41 years in 2009-10 were assessed over time. Measurements included alcohol consumption, alcohol use disorders, anthropometry, blood biochemistry, metabolic syndrome (MetS) and its individual risk factors, carotid-intima media thickness, insulin resistance, metabolomics signatures, physical activity, cardiorespiratory fitness, and other covariates.

Results: Alcohol consumption was very common in this cohort of young adults. People consuming light to moderate amounts of alcohol also had a host of other concurrent health behaviours such as better diet quality, greater amounts of total physical activity, lower prevalence of depression/anxiety compared to their non-drinker or heavy drinker counterparts. A summary of the key findings for each study are below.

Study 1: Cross-sectional analyses in 2,220 participants aged 26 to 36 years in 2004-06 showed that moderate alcohol consumption was associated with a lower prevalence of metabolic syndrome compared to light drinkers, but higher levels of blood pressure and glucose. Alcohol consumption was associated with both favourable and unfavourable effects on cardio-metabolic risk factors in young adults.

Study 2: Cross-sectional analyses in 2,220 participants aged 26 to 36 years in 2004-06, found three patterns of alcohol consumption. These patterns were not associated with carotid intima media thickness or insulin resistance, suggesting that the most common way that younger people consume alcohol was not associated with cardiovascular or metabolic health benefits.

Study 3: Cross-sectional analyses in 1,785 participants aged 26 to 36 years in 2004-06 showed that a diverse range of metabolomics signatures potentially associated with benefits and harms to health were associated with alcohol consumption. Associations with the

metabolomic profile were similar between total alcohol and types of alcohol consumed (beer and wine) and also with adjustment for a range of covariates.

Study 4: Longitudinal analyses in 2,031 participants aged 26 to 36 at baseline in 2004-06 showed that greater levels of physical activity at baseline predicted an increase in alcohol consumption 5 years later in 2009-11. In 1,322 participants at baseline in 2004-06, higher alcohol consumption predicting a decrease in total physical activity over 5 years of follow-up. There were therefore bidirectional associations between physical activity and alcohol consumption in adulthood were found.

Study 5: Longitudinal analyses in 2,239 participants showed that childhood physical activity and sport participation in 1985 was positively associated with adulthood alcohol consumption 20 years later in 2004-06. People in the middle and highest thirds of cardiorespiratory fitness (CRF) in childhood had a higher risk of being diagnosed with an alcohol use disorder (AUD) in adulthood.

Conclusions: The inter-relationships across the life course between alcohol consumption and other risk behaviours, particularly physical activity and cardiorespiratory fitness, are highly relevant to current debates regarding the nature of the association between alcohol and a range of health outcomes. The findings support recent publications demonstrating that alcohol consumption has fewer benefits for traditional cardiovascular risk factors than previous thought once potential confounders are considered. There did, however, appear to be a range of beneficial and harmful metabolic pathways associated with alcohol consumption independent of covariates. These findings may aid interpretation of recent data showing the alcohol consumption decreased the risk of myocardial infarction but increases the risk of strokes. These findings strengthen the case for modifying guidelines and public health messages regarding alcohol consumption to better acknowledge its favourable and adverse effects in relation to cardiovascular risk.

Acknowledgements

I would like to express my gratitude and thanks to all my colleagues, friends and family for their support and encouragement to complete my PhD. The work presented in this thesis would not be possible without them.

I would like to express my special gratitude and appreciation to my primary supervisor, Doctor Seana Gall for her fabulous guidance, enthusiasm, encouragement and constant support me during my work. I have really enjoyed working with you over the last three years. Thank you for your priceless support and advice. Whenever I find difficult in my study, you keep me on track. Discussing with you always solves the problem. I would like to thank you for sharing your passion in your work for medical research. I truly believe that I am now more enthused with medical research than ever before, after completing my PhD study!

I would also like to thank my co-supervisor Associate Professor Raimondo Bruno, my biostatistical advisors Professor Leigh Blizzard, Mr. Petr Otahal, Doctor Monique Breslin, Doctor Peter Wurtz from Finland. Bruno and Leigh, thank you for all the statistical advice. My love and passion for statistics have grown enormously since I have had the opportunity to work with both of you. Bruno, thank you for guiding me to develop ideas of my own. Leigh, my deepest gratitude for everything you taught me in biostatistics during the past three years. I have totally enjoyed every moment working with you. I would like to give gratitude to all other advisors, Petr, Monique, Peter for all your valuable advice during my work.

I would like to give my sincere thanks to the CDAH project leaders and members, Professor Alison Venn, Professor Terence Dwyer, Ms. Marita Dalton, Doctor Kylie Smith, Doctor Verity Cleland, Doctor Costan Magnussen, Doctor Quan Huynh, Doctor Jing Tian, as well as all the staff and volunteers. Thank you for working with me and giving me an excellent opportunity to work in the CDAH team. Professor Alison Venn, thank you for your leadership of the CDAH study and for your constructive comments for all my manuscripts. Thank you for creating such a great environment to work at Menzies and for the CDAH team! Professor Terry Dwyer, Costan and Kylie, thank you so much for your constructive comments on my manuscripts.

I would like to acknowledge the work of the CDAH study staff including Marita Dalton and Ellen Page and the team involved in the fieldwork. I would also like to thank the volunteers

that have worked on the study for over 10 years. The participants are gratefully acknowledged for their participation in the study over many years.

I would like to say a big thank to the Menzies's General Managers, Mr. Mark Bennett and Mr Peter Hicks, the Menzies's Graduate Research Coordinators, Professor Wendy Oddy, Professor Heinrich Korner and Doctor Costan Magnussen as well as all the staff in IT and administration. I received all the support I need from the Institute to complete my work.

A special thanks to my fellow PhD students for their support and for keeping me company! Thank you for sharing the ideas, discussing with me and contributing to such an enjoyable place to work at Menzies.

My love and deepest gratitude to my family, my parents, my brother and particularly Quynh and An, my beloved wife and daughter! I could keep going only because of you. Thank you for always beside me with your love and support!

Finally, I would like to express my deep thanks to all the organisations and funding bodies for giving me such a great opportunity to pursue my PhD study at the Menzies Institute for Medical Research, University of Tasmania.

Duc Du is supported by a Menzies Vietnamese Scholarship. Dr. Gall is supported by a National Heart Foundation of Australia Future Leader Fellowship (FLF 100446). The CDAH study was supported by the National Health and Medical Research Council (project grant 211316, senior research fellowship to A.V.; the National Heart Foundation (project grant GOOH 0578, fellowships PH 11H 6047 and FLF 100446 to S.L.G.) and Veolia Environmental Services.

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List of abbreviations

AB – Alcohol abuse

AD – Alcohol dependence

ASHFS – Australian Schools Health and Fitness Survey

AUC – Area under the ROC (receiver operating characteristic) curve

AUDs – Alcohol use disorder(s)

BMI – Body mass index

BP – Blood pressure

CATI – Computer-assisted telephone interview

CDAH – Childhood Determinants of Adult Health

CETP – Cholesteryl ester transfer protein

CIs – Confidence interval(s)

CIDI – the Composite International Diagnostic Interview

cMSy – Continuous metabolic syndrome risk score

CRF – Cardiorespiratory fitness

CVDs – Cardiovascular disease(s)

DALYs – Disability adjusted life year(s) lost

DBP – Diastolic blood pressure

DHA – Docosahexaenoic acid

DGI – Dietary Guideline Index

DSM-IV – the Diagnostic and Statistical Manual of Mental Disorders fourth version

DSML – Drinking self-monitoring log

EOD – Early onset drinking

FAs – Fatty acid(s)

FFQs – Food frequency questionnaire(s)

HDL-C – High-density lipoprotein cholesterol

HOMA – Homeostasis model assessment

HRQoL – Health-related quality of life

ICD-10 – the International Statistical Classification of Disease tenth version

IDF – the International Diabetes Federation

IDL – Intermediate-density lipoprotein

IMT – Intima-media thickness

IPAQ – the International Physical Activity Questionnaire

IPW – Inverse probability weighting

IQR – Interquartile range

IR – Insulin resistance

LCA – Latent class analysis

LDL – Low-density lipoprotein

MetS – Metabolic syndrome

MI – Multiple imputation

MUFA – Monounsaturated fatty acid(s)

NCDs – Non-communicable disease(s)

NCEP/ATP III – National Cholesterol Education Program – Adult Treatment Panel III

NEO – Neuroticism-Extraversion-Openness

NMR – Nuclear magnetic resonance

PWC_{170} – Physical work capacity at a heart rate of 170 bpm

PUFA – Polyunsaturated fatty acid(s)

TLFB – Timeline followback

PA – Physical activity

QF – Quantity-frequency

RAPS4-QF – the Rapid Alcohol Problem Screener – Quantity/Frequency

SBP – Systolic blood pressure

SES – Socio-economic status

TG – Triglycerides

UK – the United Kingdom

USA – the United States of America

VLDL – Very low-density lipoprotein

VO_{2max} – Maximum oxygen uptake

WHO – World Health Organization

Chapter 1

Introduction

1 Chapter 1. Introduction

This thesis presents a series of studies using data on alcohol consumption and health-related outcomes from an Australian longitudinal study that began in childhood. When the research for this thesis began in 2015, there was debate regarding the supposed health benefits of alcohol consumption. There have been several studies published in the past 12 to 18 months that address alcohol consumption and health in recognition of the need for more research in this area. The Childhood Determinants of Adult Health (CDAH) study, which included people born in the 1970s, offered an opportunity to further explore these associations.

The thesis consists of eight chapters including Introduction (Chapter 1), Methods (Chapter 2), five analytical studies conducted (Chapters 3–7), and summary, implications, future directions and conclusions (Chapter 8). The analytical studies are as follows:

- Chapter 3 describes the relationships among total alcohol consumption, types of alcoholic beverages and cardio-metabolic health in young adults.
- Chapter 4 focuses on the relationship between patterns of alcohol consumption and effects on cardiovascular and metabolic health in young adults.
- Chapter 5 addresses metabolomics signatures associated with alcohol consumption in young adults.
- Chapter 6 examines the inter-relationship of physical activity, fitness and alcohol consumption in young adults.
- Chapter 7 examines the relationships among childhood physical activity, sport participation and fitness and adulthood alcohol consumption and alcohol use disorders (AUDs).

This chapter provides an overview of the epidemiology of alcohol consumption and its association with health. It is not designed to be a comprehensive literature review but presents targeted overviews of key areas including:

(1) the levels of alcohol consumption in the population and how these change over time,
(2) predictors of alcohol consumption and how understanding these might be important for policy as well as for understanding alcohol-disease associations,
(3) burden of diseases associated with alcohol consumption,

(4) controversies regarding the health benefits of moderate alcohol consumption and health outcomes with a focus on cardiovascular disease (CVD) and diabetes, and
(5) aims and hypotheses of this thesis.

1.1. Background

1.1.1. Alcohol

Alcohol has long been a popular drink in countries worldwide. The word ‘alcohol’ is derived from the Arabic term ‘al-kuhul’ and is commonly used for a variety of alcoholic beverages such as beer, wine and spirits. One of the substances found in beer, wine and spirits is ethanol or ethyl alcohol. The simplest form of alcohol is methanol (methyl alcohol), sometimes also called ‘wood alcohol’ because it can be produced by the fermentation of wood. Other substances belonging to the alcohol group include glycol, propanol or propyl alcohol, and cholesterol–a complex molecule that is important for many bodily functions [1].

The alcohol that people drink is a special compound called ethylic alcohol (ethanol) that is made mainly from fermented starch and sugar found in many fruits and cereals. Other components in alcoholic beverages can vary depending on the type of beverage. According to the World Health Organization (WHO), alcoholic beverages processed via fermentation and distillation are divided into three categories: beer (usually having an alcohol content of 4%–5%), wine (usually having an alcohol content of 12%–15%) and spirits (alcohol content is approximately 40%) [2]. Beer is a brewed beverage often made from malt (barely germinated), hops, water and yeast [3]. Wine is an alcoholic beverage of complex composition that is obtained via the fermentation of grapes [4]. Spirits are produced from cereal starches that are saccharified, fermented and distilled prior to maturation of the spirits [5].

Different types of alcohol contain different potentially bioactive compounds that may have physiological effects. Ethanol is a common component of all types of alcohol. Beer and wine contain different bioactive compounds. Beer is a beverage rich in phenolic compounds, antioxidants and a high caffeic content [6]. Resveratrol, hydroxytyrosol and melatonin are compounds naturally present in wine [7]. The most important constituents of red wine are water, alcohol (ethanol), polyphenols, and other antioxidants [8].

It is through these different bioactive compounds that alcohol consumption may impact on physiological systems and therefore have different effects on health. In this thesis there is a focus on alcohol consumption and its association with cardiovascular and metabolic risk factors.

1.1.2. Measurement of alcohol consumption

This thesis uses data on alcohol consumption gathered during a large epidemiological study. Measures include the frequency and quantity of consumption from questionnaires and AUDs using a computerised interview. The following section provides an overview of the methods and properties of the different methods used to measure these aspects of alcohol consumption.

1.1.2.1. A standard drink

Alcohol consumption can contribute to a range of adverse health and social outcomes [9]. Hence, governments and international institutions have defined a unit called a 'standard drink' [10] to help people monitor their consumption of alcohol consistent with recommendations. Epidemiological and experimental studies use this metric to quantify consumption and assess population risk. Therefore, a standard drink size is important for population-based studies assessing alcohol-related health effects. There has traditionally been no common convention for the definition of a "standard drink" of alcohol across countries or in the literature [11]. The official definition of a standard drink is usually set by individual countries. The guidelines from the WHO on a standard drink assume that one standard drink equates to 10 grams (g) of pure ethanol, with recommendations to not exceed two standard drinks per day, with at least two non-drinking days during the week. Countries worldwide have recently adopted the WHO standard drink measure but there remains large variability between countries. The result is that a standard drink contains from 8 to 20 g of pure alcohol (pure ethanol) (Table 1-1) [10].

Table 1-1. A standard drink by countries

A standard drink by gram of pure alcohol	Countries
8	The United Kingdom
9.9	The Netherland
10	Australia, France, Hungary, Ireland, New Zealand, Poland, Spain
11	Finland
12	Denmark, Italia, South Africa
13.6	Canada
14	Portugal, The United States of America

The concept of a standard drink can be used to convert specific types of beverages, such as beer, wine or spirits, into standard amounts of alcohol [12]. The WHO guidelines defined a "standard drink" in terms of glasses of wine, beer, liquor, and shots of spirits (Table 1-2) [13]. The definition of a standard drink in Australia is a drink of alcohol equivalent to 10g of pure alcohol (or equivalent to 12.5ml of pure alcohol). Thus, one standard drink of alcohol is equivalent to 330ml of beer 5% alcohol, 100ml of wine 12% alcohol, 75ml of spirit 20% alcohol, or 40ml of spirit 40% alcohol [14].

Table 1-2. The World Health Organization's estimates of a standard drink for conventional alcoholic beverages

Type of beverage	Standard drink equivalent	Quantitative Metric
Wine	1 glass of wine; 1 small glass of sherry	140 mL (12% strength); 90 mL (18% strength)
Beer	1 can of beer	330 mL (5% strength)
Spirits	1 shot of whisky, gin, vodka; 1 small glass of liquor	40 mL (40% strength); 70 mL (25% strength)

1.1.2.2. Self-reported alcohol consumption

A previous review of the validity and reliability of self-reported drinking has been published, which showed that self-report methods are a reliable and valid approach for measuring alcohol consumption [15]. Most assessments of the validity of self-reported alcohol

consumption have focused on concurrent criterion validity comparing methods, including collateral reports, diaries, official records, interviewing methods, laboratory tests (e.g. breath, urine, blood and sweat) and multiple measures [15]. Without a 'gold standard' alcohol consumption measure to which other measures can be compared, the studies provide only limited evidence of validity. This is because two measures of alcohol use could be highly associated with each other and yet neither may be accurately assessing 'actual' alcohol consumption [15].

Food frequency questionnaires (FFQs) are a self-reported method that are widely used for measuring the usual consumption of food and beverages in epidemiological studies. FFQs are used for the assessment of dietary consumption over long-term periods, for example over a 12-month period. Several studies have shown that self-reported alcohol intake obtained via FFQs is reliable and is a valid instrument for both group and individual intake in young adults or the general population [15-18]. Measures of alcohol consumption from a FFQ are considered appropriate for accurately measuring regular consumption as well as identifying people at the extremes of intake [16-18]. Alcohol consumption measured by FFQs has been shown to be highly correlated with alcohol intakes assessed by 24-hour recalls which is a method to measure alcohol use over shorter period (Pearson's R values =0.78) [16] and a range of other measures [19]. Self-reported alcohol intake from a FFQ has also been shown to be significantly associated with potential biomarkers of alcohol consumption such as gamma-glutamyl transferase (GGT) [20]. Nevertheless, FFQs suffer from systematic and random errors [21]. For example, authors have shown that recall over longer periods of time, such as 12 months, is less accurate than over a 1-month periods in a group of women [17]. Several researchers have suggested that FFQs may provide higher estimates of consumption than other measures [22] but that correlations between measures is still high (e.g. r>0.69 for beer and wine). The reliability and validity of instruments should be considered for measuring alcohol consumption when interpreting estimated associations with different outcomes.

Other measures of alcohol consumption have also been reported in the literature including estimates of lifetime drinking, quantity-frequency (QF) methods, 24-hour recalls, 24-hour food records, alcohol timeline followback (TLFB) and drinking self-monitoring log (DSML) [23].

Measures of lifetime drinking and QF methods have similar structures. These instruments ask about average quantities and frequencies of drinking, usually over an entire drinking 'career' or very long periods [23]. These methods are recommended to obtain a lifetime or long-term

(i.e., greater than the past year) summary of alcohol consumption. They provide an overall picture of the alcohol consumption of respondents rather than a detailed daily snapshot [24, 25]. QF methods, of which there are many, inquire about 'average' or 'typical' consumption patterns, usually over a specific period. These methods, also known as estimation formulas, require respondents to report on average patterns of consumption (e.g. 'How many days *on average*—in a specific time interval—did you drink beer, and when you drank beer, *on average*, how many beers did you drink?'). Most QF methods repeat these questions for each major alcoholic beverage type (i.e., beer, wine and distilled spirits) and then sum across beverage types. QF methods generally provide reliable information about total consumption (quantity) and number (frequency) of drinking days. They are a favourable method because they are brief [26]. QF methods have similar sensitivity and specificity in terms of identifying high-risk alcohol consumers to that of FFQs but there is considerable variability [27].

The 24-hour recalls and food records are recommended to estimate an individual's intake over a short period of time, and thus they investigate current but not habitual intake. With these methods, more days of data collection are recommended to account for the variability in consumption by a person [28]. The TLFB, a daily drinking estimation method, provides a detailed picture of a person's drinking over a designated period. The TLFB method is recommended to evaluate specific changes in drinking. This method is useful when relatively precise estimates of alcohol consumption are required, especially when a complete picture of the distribution of drinking days (e.g. high- and low-risk days) is needed [29, 30]. The DSML involves recording consumption on a daily or a drink-by-drink basis. In contrast to other measures, which are retrospective, the DSML method aims to concurrently record different aspects of alcohol use (e.g. amount, frequency, moodand urges) as they occur. The DSML method is recommended for obtaining records of daily drinking reports during treatment for AUDs [31].

In summary, there are a variety of different instruments to measure alcohol consumption that are utilised in epidemiological studies. For the purposes of measuring 'regular' consumption, FFQs are an acceptable method. They demonstrate reasonable reliability and validity compared to other methods, with there being a deficiency of a 'gold standard' measure of alcohol consumption with which to compare other methods.

1.2.2.3. Alcohol use disorders

AUDs are defined as the use of alcohol that affects every day functioning. These disorders are among the most disabling disease categories for the Global Burden of Disease [32, 33]. There are two commonly used definitions of AUDs—the International Statistical Classification of Disease tenth version (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM). The two different definitions include similar items (Table 1-3). A diagnosis is usually made by a psychiatrist or other suitably qualified professional via an interview to assess whether the person meets each criterion [34].

Table 1-3. Diagnostic criteria of alcohol dependence as defined by the International Statistical Classification of Disease tenth version (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders fourth version (DSM-IV)

ICD10	DSM-IV
craving / compulsion	
impairment of the ability to control use	unsuccessful attempts to reduce or control use
withdrawal	
tolerance	
neglect of pleasures, behaviours or interests in favour of using alcohol	considerable time is spent on activities needed to obtain alcohol (discontinuation or reduction of major activities)
use of alcohol despite evident presence of harmful consequences	despite the awareness of having a persistent or recurrent problem

Recent studies have shown good agreement between the ICD-10 and the fourth edition DSM (DSM-IV) diagnostic systems for diagnosing alcohol dependence. However, there was almost no agreement between the diagnosis of alcohol abuse in DSM-IV and harmful use in ICD-10, suggesting that the two systems identify different persons reporting problems from their alcohol use [34, 35].

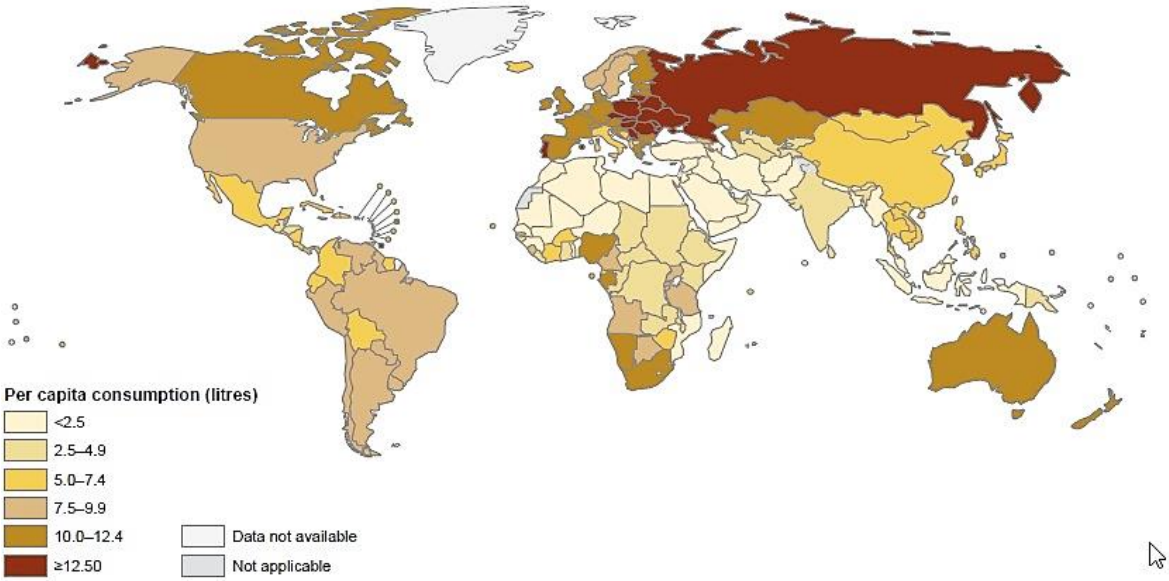
Recent studies attempting to estimate the global burden of AUDs have used a range of different diagnostic instruments. These include the alcohol module of the Composite

International Diagnostic Interview (CIDI), the Schedules for Clinical Assessment in Neuropsychiatry, and the AUD and Associated Disabilities Interview Schedule-Alcohol/Drug-Revised to Diagnose AUDs [9, 33]. These instruments require lengthy, in-depth interviews although some, such as the CIDI, can be performed using a computerised system. The resources required for these types of interviews necessitate that they are typically limited to smaller sample sizes. The CIDI has been shown to have good reliability and validity for diagnosing alcohol dependence but has poorer reliability and validity for diagnosing alcohol abuse when compared to other instruments [36].

1.1.3. Levels of alcohol consumption

1.1.3.1. Consumption of alcohol per capita

Per capita alcohol consumption worldwide is estimated to be approximately 6.2 litres of pure alcohol/person/year, which translates into 13.5 g of pure alcohol per day [2]. Of this consumption, 24.8%, or 1.5 litres/person/year, is consumed in the form of self-produced, unregistered or unrecorded alcohol. Using unregistered, self-produced alcohol can lead to an increased risk of harm because of the potential contaminants contained in the beverages. As shown in Figure 1-1, the highest alcohol consumption (10–12.5 litres/person/year) is seen in Eastern Europe, the USA, Australia and New Zealand. Lower consumption is seen in North Africa, sub-Saharan Africa and Southeast Asia (<4.99 litres/person/year) [2].



Source: Global status report on alcohol and health, 2014

Figure 1-1. Total alcohol consumption per capita (15+ years), 2010

1.1.3.2. Summary of alcohol consumption around the world

There are geographical differences in the types of alcoholic beverages consumed (Table 1-4). Spirits, which account for 50.1% of the total recorded alcohol consumed globally, are the most consumed beverage type in the Southeast Asian and Western Pacific regions [2]. Beer, the second most consumed beverage type (34.8% worldwide), is the most consumed beverage type in the Americas, North Europe and Australia. Only 8.0% of the total recorded alcohol is consumed in the form of wine. Wine is more commonly consumed in European countries and some countries in South America such as Argentina and Chile (Table 1-4) [2, 37].

Table 1-4. Types of alcoholic beverages by the WHO regions in 2010

WHO regions and Member States	Spirits (%)	Beer (%)	Wine (%)	Other (%)
African Region	7.9	33.7	6.7	51.6
Region of the Americas	32.6	55.3	11.7	0.4
Eastern Mediterranean	39.5	41.5	10.3	8.7
European Region	32.9	39.9	25.7	1.5
South-East Asia Region	77.3	22.3	0.4	0.0
Western Pacific Region	61.2	31.5	3.3	3.9
World	50.1	34.8	8.0	7.1

Source: Global status report on alcohol and health, 2014.

Most people who drink alcohol do not drink every day according to population-based surveys. The results of a study on alcohol use in 12 developing countries showed that 50% of men drank alcohol at least once a week [38]. Older people tended to consume alcohol more often than younger people [38]. For example, in Scotland, 29% of men aged 65–74 years drank alcohol more than five times a week, which decreased to only 9% in the 16–24 year age group [39].

Globally, 55% of the world's population have drunk alcohol (65% male and 45% female). The Americas, Europe and Western Pacific regions have the highest lifetime alcohol consumption in both sexes with over 70% of the population having consumed alcohol at some point in their lives. Men tend to drink more alcohol than women. In Scotland, a health survey of 6,000 households using a self-reported method by respondents to measure their alcohol consumption found that 73% of men and 59% of women over the age of 16 drank alcohol with 16% of men and 8% of women drinking at least five times a week in 2003 [39].

According to a 2001 national household survey in the United States of America (USA), 84% of the American population (over 12 years of age) have drunk alcohol. Lifetime alcohol consumption in men was 69.8% and in women was 61.5 % [40]. In 2004, 87.4% of men and 75.4% of women aged 15 and older drank alcohol in the European Union, which is the highest prevalence of alcohol use in the world. In the Americas, the prevalence of lifetime alcohol consumption was 84.8% in men and 72.6% in women. These high levels of lifetime alcohol consumption translate into low levels of abstinence. Globally, 13.1% (men: 13.8%, women: 12.5%) reported that they did not drink alcohol during the previous year [41, 42]. Southeast Asia and the Eastern Mediterranean regions had the highest rates of lifetime abstainers: 80.4% and 87.8%, respectively. In Eastern Mediterranean and Southeast Asia, the proportion of women who drink alcohol was found to be very low (6.6% and 7.2%, respectively) (Table 1-5) [42].

Another measure of alcohol consumption within a population is the age of consumption of the first alcoholic drink, which is influenced by a range of cultural and social factors. In Europe, a recent survey of 35 countries reported that the age of consumption of the first alcoholic drink was 13.6 years old for boys and 13.9 years old for girls [43, 44]. In the USA, 70% of high school students have been reported to drink beer, although the legal age for drinking is 18–21 years old (varies from state to state). Figures from the USA are similar to Europe, where the age of first consumption of alcohol was 14.0 years old in 2004–2006 [45]. In some developing countries in South America such as Porto Alegre, Brazil, the age of first alcohol consumption was very low at 10.1 years old [46]. In Australia, the average age at which Australians aged 14 years and older consumed their first serve of alcohol was 17 years. However, the average age at which 14-24 years old consumed their first serve of alcohol was 16 years [47].

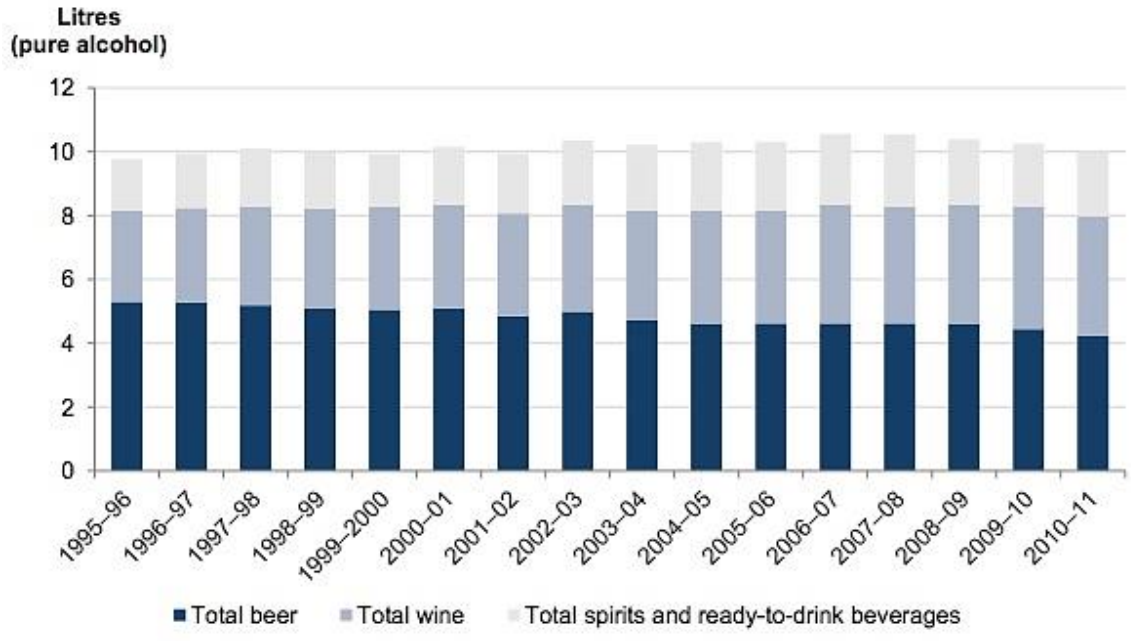
Table 1-5. The proportion of current drinkers by the World Health Organisation regions in 2004

WHO regions and Member States	Sex	Current drinkers (%)
African Region	Females	34.8
	Males	50.9
	Total	42.7
Region of the Americas	Females	72.6
	Males	84.8
	Total	78.7
Eastern Mediterranean	Females	6.6
	Males	17.6
	Total	12.2
European Region	Females	75.4
	Males	87.4
	Total	81.1
South-East Asia Region	Females	7.2
	Males	31.6
	Total	19.6
Western Pacific Region	Females	55.5
	Males	85.7
	Total	70.8
World	Females	45.0
	Males	65.1
	Total	55.0

Source: Global status report on alcohol and health, 2011.

Alcohol consumption holds an important position in social and cultural life in many countries, including Australia. The total alcohol consumption for Australians is approximately 10–12.4 litres of pure alcohol/year and has remained relatively stable in recent times (Figure 1-2). There are changes occurring in the types of drinks that consumers prefer, with wine, spirits and ready-to-drink beverages becoming more popular than beer (Figure 1-2). According to the National Drug Strategy and Household Survey in 2013, one of the most comprehensive and recent alcohol and drug-related health surveys in Australia, 89.9% of Australians aged 14 and older had tried alcohol at some time in their lives, 83% reported that they had consumed alcohol in the previous 12 months, and 6.5% reported that they drank a daily level by a self-

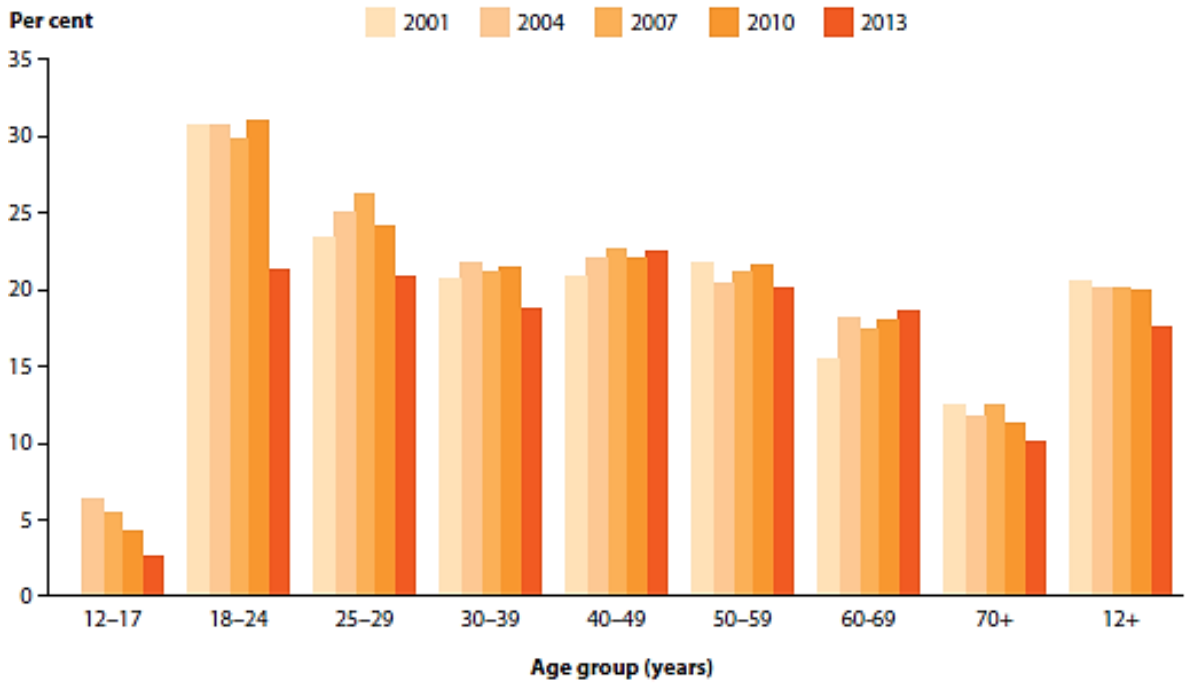
reported method [47]. Among these, 26% of men and 10% of women consumed alcohol at health risks or harmful levels over their life time [47].



Source: National Drug Strategy Household Survey in Australia, 2013

Figure 1-2. Total alcohol per capita consumption in Australia (15+ years; in litres of pure alcohol), by types of alcoholic beverages consumed, from 1995 to 2011

While most consumption of alcohol among the Australian population occurs at levels of low immediate risk, a proportion of the population drinks at levels that increase their risk of alcohol-related injury as well as the risk of developing diseases over their life course [48]. According to a National Drug Strategy and Household Survey, between 2001 and 2010 people aged 18–24 years old were the most likely age group to exceed guidelines for lifetime risk (32%). However, from 2010 to 2013, their level of risky drinking became more similar to that of older age groups. In contrast, people in their 40s were more likely to drink at levels associated with lifetime risk than any other age group. This suggests there was a transition in drinking in the young adults age groups of 20s, 30s and 40s. This highlights how young adulthood is a potentially important time to examine alcohol consumption (Figure 1-3).



Source: National Drug Strategy Household Survey in Australia, 2013

Figure 1-3. Proportion of people exceeding the lifetime risk guidelines, people aged 12 or older, by age, 2001 to 2013 (per cent)

1.1.3.3. Recommended levels of alcohol consumption

Most countries have recommended levels of alcohol use that are based on the risks caused by alcohol to people's health and social impacts. At 'safe' levels of alcohol use, health risks are at the lowest level. Recommended levels of drinking differ among countries [42]. In some countries, the recommended levels of consumption for men are higher than for women, but in others there are no differences (Table 1-6) [49].

In Australia, both men and women are recommended in current guidelines to consume no more than two standard drinks (20g or pure alcohol) on any one day to reduce the lifetime risk of harm from alcohol-related disease or injury. It is recommended that there are at least two days per week without alcohol consumption. The guidelines also suggest that people consume no more than four standard drinks on a single occasion to reduce the risk of alcohol-related injury arising from that occasion [14].

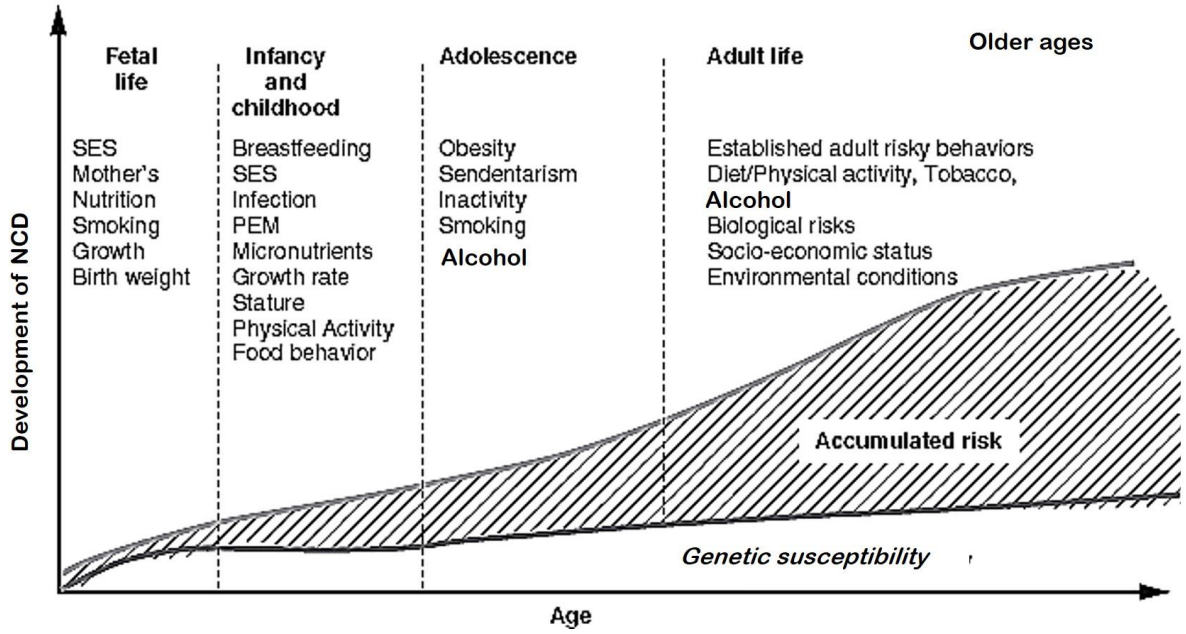
Table 1-6. Safe levels of alcohol use recommended by countries

Countries	Recommended levels (grams or pure alcohol)	
	Males	Females
Australia	20g/day	
Czech Republic	24g/day	16g/day
Finland	165g/week	110g/week
Italia	24-36g/day	12-24g/day
Japan	19.75-39.5g/day	
The Netherlands	39g/day	
New Zealand	60g/day or 210g/week	40g/day or 140g/week
South Africa	252g/week	168g/week
Sweden	20g/day	
The United Kingdom	32g/day or 168g/week	24g/day or 112g/week
The United States of America	42g/day or 196g/week	28g/day or 98g/week

Source: International Centre for Alcohol Policies report, the USA 2003.

1.1.4. Alcohol consumption across the life course

There is increasing recognition of the importance of examining non-communicable diseases (NCDs) using a life-course approach [50]. As shown in Figure 1-4, the life-course approach to NCD prevention considers the influence of different risk factors at each stage of the life course. It allows for consideration of how a risk factor may influence health differently depending on the period of exposure including via changes in the level of the risk factor and also accumulation of risk overtime (Figure 1-4) [50].



Source: Adapted from Aboderin et al. (Darnton-Hill, Nishida and James, 2004)

Figure 1-4. Scope for non-communicable diseases prevention – a life course approach

Life course epidemiological studies have tracked long–term changes in alcohol consumption and related behaviours or outcomes. These data can be used to detect trends in consumption among the population or certain subgroups, to examine alcohol-related outcomes, and to understand the consequences of interventions. Changes of alcohol consumption over time can be assessed at two levels: the individual level and the population level. Changes at the individual level can be monitored by diary, longitudinal, or retrospective surveys in which data are collected on the same individuals at different points in time using methods discussed in a previous section. Changes at the population level can be collected by evaluating aggregate or survey data collected at periodic intervals for a population where the definition of consumption remains constant but whose members change over time (e.g., people age 14 and older, or adults age 18 and older) [51].

Several longitudinal studies have shown that long-term alcohol consumption trajectories differ across the life course. Most of these studies are conducted in the context of understanding health effects of alcohol consumption. For example, a recent meta-analysis of six cohort studies (five British and one French) using data of 35,132 individual participants with assessment of alcohol at 3 times over a 10 year period showed that drinking behaviours were unstable over time using adherence to low risk drinking guidelines over time [52]. This resulted in categories including consistent non-drinker, former drinker, consistently moderate, inconsistently moderate, consistently heavy and

inconsistently heavy. The proportion of people in each category was different for men and women. In men, the most common group was consistently moderate (41%), followed by inconsistently moderate (20.4%) and consistently heavy (12.5%). In women, the most common group was also the consistently moderate (38.8%), followed by former drinker (21%) and inconsistently moderate (19%). The authors reported that individuals who abstain from drinking (either non-drinker or former categories) and those who had inconsistently moderate alcohol consumption had a higher risk of fatal or non-fatal CHD [52]. In a case-cohort study of people in the Whitehall study in the United Kingdom (UK), 8,292 participants had self-reported alcohol consumption recorded at 6 different periods over 28 years. The authors reported that there were different trajectories of drinking for men and women with these differing by type 2 diabetes diagnosis later in life. For example, men that went on to develop type 2 diabetes had a stable increase in consumption prior to diagnosis whereas those that did not develop type 2 diabetes tended to have an increase followed by a decrease over time. Few men 'quit' drinking but more women did quit, particularly those that went on to develop type 2 diabetes [53]. Few studies have focused specifically in younger people, which is surprising given that population-level data suggest that this group have considerable changes in their consumption. In one 22-year longitudinal study in the U.S. examined alcohol use trajectories across 6 assessments from adolescent age of 14 to adulthood age of 36 in the context of cannabis use disorders in adulthood [54]. The authors found that there were three trajectories that described alcohol consumption: increasing alcohol use (9%), no or low alcohol use (8%) and moderate alcohol use (83%). Increasing or moderate groups, compared to no or low use were associated with cannabis use disorders at follow-up.

These findings suggest the importance of tracking alcohol consumption over time, particularly in the context of effects on health outcomes. There are few studies focused on younger populations.

1.1.4.1. Predictors of alcohol consumption at early stages of the life course

There is a substantial body of literature examining a range of predictors of alcohol consumption among children and adults. Analyses within this thesis focus on some specific predictors from childhood and adulthood. This section provides an overview of the major predictors of alcohol consumption and AUDs in children and adults.

Early onset drinking (EOD) in childhood and adolescence is a risk factor for adult alcohol and drug abuse/dependence [55]. Evidence has shown that EOD is a significant predictor of problem drinking behaviour in adolescents, young adults and older adults. Epidemiological studies have reported that greater than 95% of 12–17-year-olds in Denmark, Greece, the Czech Republic, and the Slovak Republic have consumed alcohol to some extent [56]. Moreover, recent studies have identified substantial alcohol use in children under the age of 12 [57] and even as young as 8 [58]. Donovan [59] found that, in the USA, nearly 10% of the 10-year-old group, 16% of the 11-year-old group, and nearly 30% of the 12-year-old group had consumed more than just a sip of alcohol. Likewise, Picherot et al. [60] used data from two European school surveys conducted in 2005–2006 and in 2007 reported that 59% of the 11-year-old group, 72% of the 13-year-old group and 84% of the 15-year-old group admitted to consuming alcohol in their lifetime.

There are known risk factors for EOD. Zucker [61] and Zucker et al. [62] summarised risks in the following three domains: (a) Individual differences in temperament and behaviour, (b) environmental influences and (c) genetic influences. Together, these three domains interact and predict alcohol use initiation at an early age. For each of these domains, Table 1-7 provides an abbreviated list of risk factors that are associated with EOD.

Table 1-7. Risk factors for early onset drinking

Domain	**Nonspecific risks**	**Alcohol-specific risks**
Individual differences in temperament and behaviour	– Aggressiveness – Delinquent, conduct disordered, and antisocial behaviour – Behavioural under-control/ disinhibition – Impulsivity/risk Taking – Sensation seeking – Reward responsivity – Anxiety/depression – Deficits in attention – Low resiliency – Sleep difficulties	– Positive beliefs and expectancies about alcohol

	– Social inhibition/shyness	
Environmental factors	– Abuse	– Fatal alcohol exposure
	– Family conflict	– Mass media
	– Selected minority group affiliations (some are protective)	– Modelling of heavy drinking by parents and/or peers
	– Poor parental monitoring	– Geographic clustering of heavy drinkers
	– Poor/neglectful parenting	– Easy alcohol availability
	– Low socioeconomic status	
Genetics	Heritable pathways for	– Ethanol metabolism
	– behavioural under-control/disinhibition	– Sensitivity of response to ethanol
	– delayed aversion/reward response	
	– negative affect expression	
	– aggressiveness	

Source: Zucker RA et al., 2006 and Zucker RA et al., 2008.

Previous studies have shown that EOD in childhood was associated with alcohol-related problems in adulthood. Predictors include earlier age of first drink, childhood psychiatric and psychosocial factors, familial background and influence, and lower/higher socio-economic status (SES) [63-67]. However, there is lack of comprehensive research on the multi-stage process from childhood through to adulthood, particularly regarding predictors at each stage of the life course. In addition, the period of risk for developing dependence to alcohol following the initiation of alcohol use is long compared to the risk period for other drugs [68]. This suggests that it is important to investigate mechanisms underlying the development of AUDs.

1.1.4.2. Alcohol consumption and other health behaviours

There are complex relationships between alcohol use and other socio-demographic factors such as age, sex, SES, education level, occupation and marital status. For example, in Australia, compared to drinkers, the non-drinkers were more often female, more likely to be

married, pregnant, non-smokers, born in non-English speaking countries, to live in the Northern Territory, and to have lower levels of education and employment [69].

Health behaviours such as alcohol consumption often co-occur with other health behaviours [70]. Together these clusters of health behaviours can jointly contribute mortality and morbidity from a range of diseases [71, 72]. Alcohol consumption is known to often co-occur with smoking [73], physical activity [74], and dietary intake [75]. The clustering of health behaviours may cause difficulty in understanding causal associations between behaviour and health outcomes. In this thesis, there is a specific focus on the inter-relationships between physical activity, fitness and alcohol consumption.

The inter-relationship between physical activity (PA) and alcohol consumption in modifying the risk of disease has been suggested by some researchers [76, 77]. Physical activity provides a wealth of benefits to health, providing protection against a range of diseases [78]. In contrast, alcohol consumption is not typically regarded as a health-promoting behaviour and there is ongoing debate about the health benefits of moderate alcohol intake, particularly for CVD [79-81].

There is evidence indicating a complex relationship between alcohol use and physical activity. Some studies showed a positive linear association between PA and alcohol [82, 83], but others have found no association [84, 85]. Several studies have shown a positive linear association between total physical activity (e.g. leisure time, work and transport physical activity combined) and alcohol consumption [82, 83]. For example, in a cross-sectional study of people in the United States (US), it was reported that higher levels of daily alcohol consumption and occasional binge drinking measured by questionnaires were associated with higher minutes of total physical activity per week measured by questionnaire [82]. Similarly, a cross-sectional study of men and women aged 17-38 years old in Greece showed that higher alcohol consumption per week assessed by a daily drinking questionnaire were associated with higher levels of weekly physical activity also assessed by questionnaire [83]. In contrast, cross-sectional and longitudinal analyses among the Finnish adult population revealed that weekly alcohol consumption was not associated with frequency of total physical activity [84]. A limitation of previous findings is that most previous research has examined the influence of subjective self-reported physical activity and adult alcohol consumption. There has been limited insights into specific types of physical activity or objective measures of physical activity and alcohol consumption, particularly in longitudinal studies. It is possible that deeper

examination of the association between types of PA and alcohol consumption could further our understanding of the relationship.

The role of physical activity in childhood on alcohol consumption in adulthood has been examined in some studies. Longitudinal studies have shown that physical activity in childhood or adolescence reduced the risk of AUDs in adulthood. For example, persistent physical inactivity in adolescence was associated with a 2-fold increased risk of alcohol use problems later in life compared to being persistently active in a study of 4,240 people in Finland followed from the age of 16–18 years old to the age of 22–27 years old [86]. Similarly, a recent finding from a cohort study of 18,359 people in Denmark followed for 20 years showed that higher leisure time physical activity during early life (20 years and above) appeared to be protective against AUDs later in life [87]. The study showed that people that did more minutes/hours of leisure time physical activity early in life measured with a questionnaire had an almost half lower risk of developing AUDs than those that did less leisure time physical activity. It has been proposed that social-demographic characteristics, personality, biological and social mechanisms might explain the association rather than there being a direct causal link between AUDs and physical activity [88]. However, few studies have been able to control for a wide range of potential explanatory factors; therefore, the mechanisms remain unknown [85, 88]. Studies of the association have tended to examine total or leisure time physical activity [86, 87]. It is possible that deeper examination of the association between types of physical activity and alcohol consumption could further our understanding of this relationship. Similarly, examining the role of physical activity in childhood on adult alcohol consumption may help us understand the nature of this association; however, few studies of this type exist [86].

Participation in sports – a specific and popular type of physical activity – has also been associated with alcohol consumption, although the associations have been variable. Cross-sectional studies showed that participation in sports was associated with lower [89, 90] or higher levels of alcohol use [91, 92], but others found no association at all [93] among adolescents. In one cross-sectional study of 460 people aged 16-24 years old in France it was found that, compared to individual sport, participation in team sports was positively correlated with alcohol use [90]. Greater childhood sport participation measured using questionnaires in approximately 1,000 children aged 12 years old was associated with greater adulthood alcohol consumption measured at aged 18 years and at aged 28 years old but the authors suggested that this was not necessarily a direct effect [94]. The authors concluded that the apparent

association between sport activity and alcohol consumption was likely mediated by other factors such as the availability of alcohol, personal beliefs and impulse control but that study did not have measures of those variables [94]. There is a need for more longitudinal studies from childhood to adulthood with a range of potential explanatory factors to better understand the nature of this association to potentially improve interventions to address drinking in sports clubs.

There is a need for more information regarding the association between physical activity and alcohol consumption because this is important for correctly estimating the associations between alcohol consumption and health outcomes. It may also be important for updating public health guidelines around alcohol consumption, as well as interventions at the population-level to address alcohol consumption and, potentially, physical activity.

1.1.5. Effects of alcohol on health

The consumption of alcohol has both short-term and long-term effects on health. Alcohol-related harm in individuals arises not only from the quantity of alcohol consumed but also from a complex interaction between the age and experience of drinkers, their social environment, genetics and general health [14].

1.1.5.1 Metabolism of alcohol

Alcohol enters the bloodstream through the stomach and small intestine after consumption. If there is food in the stomach, the penetration of alcohol into the blood occurs more slowly. Alcohol is mostly excreted in the body via the liver (91%) with smaller proportions excreted in the urine (3%), sweat (3%) and breath (3%). It takes the liver approximately one hour to metabolise 10 g of pure alcohol, e.g. one standard drink [1, 95]; however, this rate varies from person to person. The rate of metabolism depends on several factors including liver size, body mass and composition, and alcohol tolerance [96]. Differences in the speed of alcohol metabolism between people are also related to individual variation in the genes that control expression of alcohol-metabolising enzymes in the liver [96, 97].

Alcohol is a powerful psychoactive substance. Heavy alcohol use causes several psychiatric disorders; however, consumption within normal ranges also affects the nervous system in several ways. The most immediate effects of alcohol are on the brain, beginning with feelings of relaxation, wellbeing and loss of inhibitions. As the intake of alcohol increases, these

effects are counterbalanced by less pleasant effects, such as drowsiness, loss of balance, nausea and vomiting [14]. Potentially adverse physiological effects of alcohol begin with dampening of the brain's arousal, motor and sensory centres, which reduces reactions to stimuli and affects coordination, speech, cognition and the senses. Alcohol can also affect the pituitary gland, suppressing the production of the anti-diuretic hormone. This causes the kidneys to fail to reabsorb an adequate amount of water and results in dehydration [14]. These effects increase the risk of accidents and injury during and immediately after drinking. Every additional drink significantly increases the risk of injury and death for the drinker and may place others at risk of harm as well. Alcohol consumption also increases the likelihood and extent of aggressive behaviours and reduces the cognitive or verbal capacity to resolve conflicts, thereby increasing the likelihood of physical violence (e.g. fights and assaults) [98, 99].

There is considerable evidence that alcohol consumption is associated with a higher risk of cancer [100], digestive diseases including those of the liver [101], intentional (e.g. self-inflicted injuries, homicides, suicide) and unintentional (e.g. car accidents, falls, fires, drowning) injuries, as well as skin diseases such as psoriasis and long-term cognitive impairment [14]. Alcohol consumption therefore affects a range of physiological systems and has therefore been associated with a range of diseases that may cause death and adverse effects that reduce quality of life.

1.1.6. Burden of alcohol-related disease and injury

The overall effects of alcohol consumption on health can be measured in terms of its association with incidence, prevalence or mortality from diseases it is causally associated with and the associated economic costs. This thesis focuses on risk factors associated with cardiovascular and metabolic diseases; therefore, this section provides a summary of studies where the effects of alcohol consumption on incidence, prevalence and mortality of these diseases has been examined. Literature focused on the relationship between alcohol consumption and risk factors for associated diseases is also summarised.

The burden of alcohol-attributable diseases and deaths is an important issue in most countries. Alcohol consumption has been identified as the leading risk factor associated with death and morbidity globally, accounting for 5.9% of death and 4.1% of disability adjusted life years (DALYs) lost in 2014 globally [2]. In terms of DALYs lost in 2011, alcohol ranked third highest (first highest in middle-income countries, second highest in high-income countries

and eighth highest in low-income countries). Several studies have concluded that there is an association between alcohol consumption and over 60 different diseases [37, 41]. In terms of NCDs, alcohol has been linked particularly to cancer, CVDs and liver disease [33, 102]. Alcohol is also involved in many social problems, including violence, neglect and child abuse. However, despite all these issues, excessive alcohol use restrictions are not yet one of the priorities of public policies, including health policies [42].

Alcohol consumption has been an important risk factor for a range of diseases that may cause death and reduce quality of life; however, nature of the risk appears to depend on the amount consumed. Many studies have reported a J-shape association between alcohol consumption and all-cause mortality, which suggests a potential beneficial effect of light to moderate alcohol consumption; however, these beneficial effects remain controversial [79, 103, 104]. As noted elsewhere, researchers have raised concerns about the possibility of selection bias, competing risks related to diseases occurring later in life [79], inappropriate selection of a reference group or weak adjustment for confounders [104] in studies of alcohol consumption and health outcomes.

AUDs are major public health issues worldwide, including in Australia. According to the WHO global status report on alcohol and health in 2014, the prevalence of AUDs (a past 12-month estimation for those aged 15+) was 5.0% for males and 2.1% for females among the Australian population. The estimated figure for the Western Pacific Region, of which Australia is a part of, was 4.6% [105]. The Australian National Survey of Mental Health and Wellbeing reported that AUDs (using DSM-IV diagnosis criteria over the previous 12 months, including alcohol abuse or alcohol dependence) were among the most prevalent disorders in the Australian population (6%). They were most likely to occur among males aged 18 to 24 years old. AUDs were associated with high rates of other substance use and mental health problems than occur in people without AUDs [35].

Alcohol consumption is associated with a range of costs to society including direct costs to justice and social welfare systems, as well as to the health system. It is estimated that countries spend approximately 2%–5% of their gross domestic product on issues associated with alcohol. Some countries have had social spending on alcohol of up to $6 billion USD (Japan) or $190 billion USD (the USA), of which 20% are for direct costs such as medical services, social and legal matters; 10% are for physical damage costs; and 70% are for the cost of alcohol induced premature death, loss of employment and reduced productivity [106]. In Australia, the total costs to society of alcohol-related problems in 2010 was estimated to be

$14.352 billion AUD. Of this, $2.958 billion (20.6%) represents costs to the criminal justice system, $1.686 billion (11.7%) comprises costs to the health system, $6.046 billion (42.1%) involve costs to Australian productivity and $3.662 billion (25.5%) are costs associated with traffic accidents. Productivity losses accounted for the largest proportion of the total cost estimate—with these losses calculated as the sum of reduced workforce and household labour due to premature mortality, reduced household labour due to sickness and reduced workforce participation due to absenteeism [107].

Alcohol consumption contributes significantly to the burden of disease in Australia and globally. There should be efforts to understand how alcohol consumption changes over the life course and its association with health outcomes to identify ways to potentially modify this burden.

1.1.7. Alcohol consumption, cardiovascular and metabolic diseases

While there are clear links between higher alcohol consumption and a range of different diseases, there is also a large body of literature suggesting that moderate levels of consumption may be associated with a lower risk of mortality and morbidity, particularly for CVDs. There is considerable controversy regarding these potential benefits of alcohol consumption for cardiovascular and metabolic health. This section summarises the literature regarding the role of alcohol in the development of these diseases.

1.1.7.1. Association between alcohol consumption, cardiovascular and metabolic diseases

When the research for this thesis began in 2015 there was a large body of literature suggesting that moderate levels of consumption of alcohol were associated with cardiovascular health benefits. These epidemiological studies had reported the relationship between alcohol consumption and all-cause and specific-cause mortalities as a J-shaped curve, in which moderate drinkers (usually cut-off of 10-20 g/day) had the lowest risk compared to abstainers or heavy drinkers (≥30 g/day) [79, 80, 104, 108, 109]. Similarly, several studies had also suggested a J-shape association between alcohol consumption and the risk of developing type 2 diabetes with a protective effect of light to moderate alcohol consumption compared to non-drinkers or heavy drinkers [103, 110, 111]. Many authors had, however, raised concerns on the possibility of selection bias, competing risks related to diseases occurring later in life [79], inappropriate selection of a reference group or weak adjustment for confounders [104]. For example, the authors of a recent systematic review of studies investigating alcohol use and

mortality suggested using occasional drinkers as the comparator instead of abstainers because abstainers often include former drinkers and people who have stopped drinking owing to health issues, thus creating a bias that made light drinkers appear healthier in comparison [80]. A further issue with existing studies [109] [112-114] is the limited control for the potential confounding effects of dietary intake, physical activity, cardiorespiratory fitness (CRF) and mental health, which are strongly associated with alcohol consumption [74, 76] and cardio-metabolic risk factors [115]. In addition, most authors have focused on adults and older individuals [79, 80]. The differing results between studies could be due to older individuals in whom the recall of alcohol consumption across the life course might be unreliable [116] and co-morbid diseases influencing associations [79].

Recent publications including new epidemiological studies and reviews on alcohol consumption and a range of health outcomes have contradicted these previous studies. These new studies have shown that low-volume alcohol consumption has no net mortality benefit compared with lifetime abstention or occasional drinking [117, 118].

1.1.7.2. Associations between alcohol and cardiometabolic risk factors

In addition to the associations with disease outcomes, research has also been conducted on the relationship between alcohol consumption and risk factors associated with these diseases. Observational studies have revealed negative associations between alcohol consumption and other strong predictors of future cardio-metabolic diseases such as the prevalence of metabolic syndrome (MetS) [119], lipidaemia including high-density lipoprotein cholesterol (HDL-C) and triglycerides [120], glucose metabolism, blood pressure, or predictors of future coronary and cerebrovascular events such as carotid intima-media thickness [121, 122]. Comprehensive reviews of the association between alcohol and these risk factors were undertaken with the methods presented in Appendix 1A, along with the summary tables of results (Table 1-8 to Table 1-13).

Alcohol and metabolic syndrome

MetS is defined as the combination of individual components leading to metabolic abnormalities including central obesity, dyslipidaemia, hypertension, insulin resistance (IR), impaired fasting glucose and glucose intolerance [123]. The syndrome has become one of the major global health problems with a remarkably increased prevalence worldwide over the last two decades [123]. In addition, it is known as a strong predictor of the development of CVD,

type 2 diabetes, and all-cause mortality in non-diabetic individuals. Previous published studies that have mostly drawn on samples of adults or older aged groups or in the general population have shown that the relationship between alcohol consumption and MetS is inconsistent (Table 1-8). Some studies revealed an inverse association (protective effects of alcohol) [114, 124-128], whereas others have reported a positive association (risk effects of alcohol) [77, 116, 129-136], a J-shaped association [113, 114, 135, 137-142] or no relation at all to MetS [124, 138]. Meanwhile, a considerable amount of literature has been published on a J-shaped association between alcohol consumption and the risk of MetS development, in which low-to-moderate alcohol intake has been reported to decrease the risk of MetS, whereas high levels of alcohol intake have increased the risk [113, 114, 137, 139]. For example, Gigleux et al. in 2006 reported that data analysis from a Canadian male cohort from a Quebec cardiovascular study showed that increased levels of alcohol consumption were dose-dependently associated with lower incidence of MetS across all quartiles of drinking [127]. A cross-sectional analysis of data of 8,125 participants ages 20 years or older from a national health and nutrition examination survey conducted in the USA showed that mild-to-moderate consumption but not abstinence or heavy alcohol consumption was associated with a lower prevalence of MetS [125]. In contrast, several studies have reported that alcohol consumption was associated with a higher risk of developing MetS [134-136]. These studies may have found different results because of the complex mechanistic relation between alcohol consumption and each component of MetS. The contrasting results may also be due to differences in the types or patterns of alcohol consumption, as well as the effects of confounding factors particularly lifestyle factors that may be associated with both alcohol consumption and cardiovascular or metabolic risk factors.

Alcohol and obesity

The association between alcohol consumption and obesity was not consistent between different studies (Appendix Table 1-9). Some studies demonstrated that light to moderate alcohol consumption was associated with a lower risk of obesity whereas non-drinking and heavy alcohol drinking was associated with an increased risk of being obese [128, 135, 137]. In contrast, several other studies have reported that alcohol consumption is positively associated with obesity [77, 134]. For example, a USA study of 7,483 men ages 20–100 years old observed that light to moderate alcohol consumption (1–7 drinks/week) was significantly associated with a lower risk of having central obesity whereas heavy alcohol consumption (14+ drinks/week) was not associated with such a lower risk after adjustment for covariates

[128]. Baik et al. [134] reported that light, moderate or heavy drinking were positively associated with obesity or high body mass index (BMI) in 3,853 participants ages 40–69 in a Korean population study (Appendix Table 1-9). The associations between alcohol consumption and obesity are inconsistent but the association is potentially important for understanding the mechanisms linking alcohol consumption to other health outcomes.

Alcohol and lipidaemia

There is a considerable number of studies in the literature that have shown that alcohol consumption was significantly associated with a lower risk of low HDL-C levels in a dose-dependent manner (Appendix Table 1-10). For example, the risk of low HDL-C levels decreased by 50% with one drink/day and to 75% with two drinks/day on average [124, 125, 137]. Only some of the mechanism(s) by which alcohol influences the serum HDL concentrations are known. Alcohol intake may raise HDL by altering the synthesis or clearance of HDL or by effects on enzymes and proteins influencing HDL metabolism. Cholesteryl ester transfer protein (CETP) mediates the transfer of cholesteryl esters from HDL into very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) with a reciprocal exchange of triglycerides [143].

Alcohol consumption has been reported to be associated with elevated plasma triglycerides, however the effects of long-term alcohol consumption are inconsistent (Appendix Table 1-11). The relation between alcohol consumption and serum triglyceride levels has been previously reported as ‘not significant’ [77], ‘positive’ [127, 128] or ‘J-shaped’ [134]. For example, it was reported that 1–2 drinks/day was modestly associated with lower risk of hypertriglyceridemia (10%), but that alcohol consumption above two drinks/day was associated with an increased risk of hypertriglyceridemia in a dose-dependent fashion [137]. Other studies showed an inverse relationship between long-term, moderate alcohol consumption and fasting triglycerides [128, 134]. Another study reported that when consumed in amounts of more than 60 g/day, alcohol has a hypertriglyceridemia effect, and triglyceride concentrations increase by 0.19 mg/dL per gram of alcohol consumed per day [144].

Newer profiles of lipids available through metabolomic analyses may provide a better way to understand the complex interactions between alcohol consumption and lipids. In the single study conducted to date, authors from Finland examined alcohol consumption and lipids using the serum nuclear magnetic resonance (NMR) platform. They found that most lipid measures displayed U-shaped associations with alcohol consumption, whereas the strongest biomarkers

of alcohol intake followed linear shapes, including for HDL cholesterol [145]. These findings revealed complex relationships between alcohol and lipidaemia and these relations play a key role for understanding the effects of alcohol on metabolic and other health outcomes. Confirmation of these findings in other cohorts are warranted.

Alcohol and high blood pressure

There is consistent evidence of elevated blood pressure associated with moderate-to-heavy alcohol consumption, whereas findings regarding light drinking have shown lower, higher or no difference in blood pressure compared with abstaining from alcohol (Appendix Table 1-12). Previous studies have shown that the risk of high blood pressure was associated with increased alcohol consumption [146, 147]. In a meta-analysis that looked at the association of alcohol consumption and the risk of 15 diseases, different doses of alcohol were associated with greater risks of hypertension: 25 g/day, relative risk (RR) 1.43 (95% confidence interval [CI] = 1.33–1.53), 50 g/day, RR 2.04 (95% CI 1.77–2.35) and 100 g/day, RR 4.15 (95% CI 3.13–5.52) [148]. In another meta-analysis of randomised controlled trials, alcohol reduction, i.e. reducing alcohol intake by an average of 67% (from 3.06 drinks/day to 1–2 drinks/day), reduced systolic blood pressure (SBP) by 3.3 mmHg and diastolic blood pressure (DBP) by 2.0 mmHg [146]. Fan et al. [126] also reported that in current alcohol drinkers compared to non-drinkers SBP was increased by 3.78 mmHg and DBP by 4.06 mmHg in a sample of 3,953 people in China assessed in a cross-sectional study. In contrast, a J-shaped relation between alcohol and blood pressure has also been suggested with moderate drinkers having a lower blood pressure level, with the lowest levels in those who consume 1–2 drinks/day [124, 137]. It has been demonstrated that, compared with non-drinking, minimal drinking lowers the risk of hypertension among women [149], but elevates the risk among the USA white [129] or Japanese population [114]. There is therefore a complex association between alcohol consumption and blood pressure.

Alcohol and glucose metabolism

The results of previous studies relating alcohol consumption to glucose and the risk of type 2 diabetes are conflicting (Appendix Table 1-13). A meta-analysis based on prospective studies suggested that there is a U-shaped relationship between alcohol consumption and type 2 diabetes, with people consuming moderate amounts of alcohol having the lowest risk of developing type 2 diabetes [150]. However, several cross-sectional evaluations of healthier populations have reported higher fasting glucose concentrations and greater risk of diabetes

associated with alcohol consumption [151]. In contrast, alcohol consumption has also been found to be associated with lower insulin concentrations [125, 152]. These discrepant results may be due to the different beverage types because heavy liquor consumption has been shown to increase the risk of type 2 diabetes, whereas similar amounts of beer and wine have not [153]. Excess alcohol consumption is associated with the risk of developing type 2 diabetes because heavy alcohol intake can cause metabolic abnormalities due to liver cirrhosis.

Moderate alcohol consumption is reported to be associated with a decrease in insulin resistance [154]. Randomised placebo-controlled trials in non-diabetic individuals showed that two drinks/day was associated with significantly lower fasting insulin, postprandial insulin levels and an increase insulin sensitivity [155]. The mechanism by which alcohol might increase insulin sensitivity remains unclear. McCarty [156] proposed that the metabolism of acetate from alcohol in peripheral tissues generated sufficient levels of adenosine monophosphate (AMP) to temporarily stimulate the AMP-activated protein kinase, which in turn induced the synthesis of certain long-lived proteins that act to boost insulin sensitivity and possibly aid the efficiency of fat oxidation. The suppression of fatty acids (FA) release from adipose tissue by alcohol might be another mechanism by which alcohol improves insulin sensitivity [157]. This reduction in FA decreases substrate competition in the Krebs cycle of skeletal muscles, thereby facilitating glucose metabolism [157].

In summary, there remain inconsistencies regarding the association between alcohol consumption and cardiovascular or metabolic risk factors. There is a preponderance of studies in men [77, 112, 128, 133, 136, 142] despite evidence that women [113, 114, 127, 137], particularly at younger ages, are consuming similar amounts of alcohol to men. The studies also generally focus on people in middle age or older [112, 113, 125, 133-135, 137] where co-morbid disease or risk factors may make it difficult to interpret the associations between alcohol and different health outcomes. Studies on older individuals may under or overestimate associations because of difficulties with recall of alcohol consumption across the life course. It is possible that further investigations of the younger population might overcome these limitations. Although authors have included a variety of potential confounders in multivariable models, residual confounding is still possible. There are other factors including lifestyle factors (with regards to diet, physical activity), CRF and genetic factors that related to both alcohol consumption and cardiovascular and metabolic risk factors that were not considered [112, 125, 126, 128, 131, 137, 142] (Appendix Table 1-8 to Table 1-13).

1.1.7.3. Associations between alcohol consumption and cardiorespiratory fitness

As noted earlier, there has been recent recognition of how physical activity and alcohol consumption may jointly modify the risk of disease [76, 77, 158]. When examining the association between physical activity and alcohol consumption, the potential role of CRF should be considered. CRF is strongly associated with the incidence of cardiovascular [159] and metabolic diseases [160]. It is a measure of the capacity of the cardiovascular system to transport oxygen and the capacity of the muscle to use it. CRF is measured by peak exercise oxygen uptake (VO_2) [159]. A person's CRF reflects genetic, environmental or behavioural factors [75]. CRF can be modified by increased or decreased participation in physical activity [159]. For example, CRF is known to be associated with self-reported physical activity and sport participation among children [161]. Of relevance to studies of alcohol consumption and physical activity is that some cross-sectional studies among general population have reported that alcohol consumption has a U-shaped association with CRF [75, 162]. In contrast, other cross-sectional and longitudinal studies of adults reported no association [163, 164]. There is currently uncertainty regarding the mechanisms linking alcohol and CRF. Previous studies have tended to be cross-sectional [75, 162], thereby preventing examination of any temporal sequence between alcohol consumption and CRF. Evidence from longitudinal studies is required to examine the nature of this association. Understanding the inter-relationship between alcohol consumption, physical activity and fitness may help us better understand the recent findings refuting the health benefits of moderate alcohol consumption [80, 117]. The roles of physical activity and CRF in childhood in predicting alcohol consumption in adulthood are unknown. Examining the relationships between childhood CRF and adulthood alcohol consumption with consideration of potential explanatory factors should provide a better understanding of the nature of these associations and the development of alcohol-related risk factors and diseases.

1.2. Aims of this thesis

Among the few international longitudinal studies with the capacity to measure risk factors at different life-stages, the CDAH study in Australia that utilised repeated measures over life courses provides an opportunity to examine the effects of alcohol consumption on cardiovascular and metabolic risk factors with consideration of important confounding or mediating variables including physical activity and fitness.

The conceptual framework shown below reveals the potential mechanism needed to further investigate the link between alcohol and risk factors from early stages of the life course in the development of alcohol-related biomarkers and diseases (Figure 1-5). Due to the availability of the data from the CDAH study, this thesis focuses on the investigation of the association between alcohol consumption and CVD and metabolic risk factors in young adults when they were aged 26-36 years old (CDAH-1) and the inter-relationships between alcohol consumption and other health behaviours including physical activity and CRF from childhood (7-25 years old) to adulthood. There was no information on CVD risk factors when participants were aged 31-41 years old (CDAH-2). Longitudinal studies with potential on-going data from the next follows-up periods of the CDAH study (CDAH-3) into older aged adults are needed to investigate the relationship of childhood risk factors including physical activity and CRF with alcohol consumption and alcohol use problems in late adulthood and the associations between alcohol consumption and major CVD and metabolic risks and events later in life.

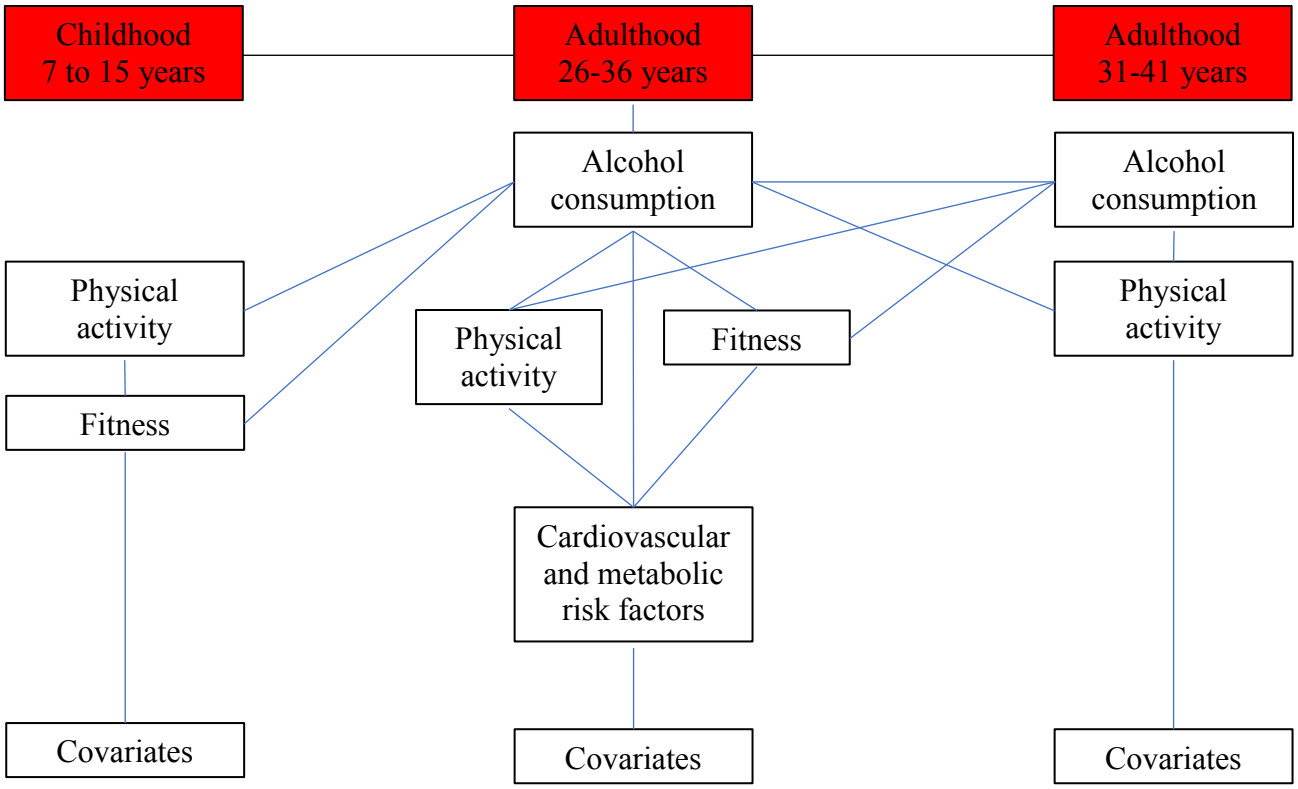


Figure 1-5. Conceptual framework on the relations between alcohol and risk factors in the development of diseases across the life course

The aims of this thesis are to:

- Examine the associations among total alcohol consumption of different types of alcoholic beverages and cardio-metabolic health in young adults, and investigate the possible mechanisms underlying any association.
- Examine the association between the overall pattern of alcohol consumption and health effects in young adults, and investigate the possible mechanisms underlying any association.
- Examine a diverse range of metabolomics signatures associated with alcohol consumption in the development of health outcomes.
- Examine the inter-relationship of physical activity, fitness and alcohol consumption in young adults, and investigate the possible mechanisms underlying any association including life-stage transition.
- Determine whether childhood physical activity, sport participation and fitness predict adulthood alcohol consumption and AUDs, and whether it does so independently of confounding factors in childhood and adulthood.

1.3. Appendix 1.A. Additional Methods

The review presented in section 1.1.7 above was drawn on manual and computer searches in several bibliographic databases including PubMed (NLM), National Library of Medicine, and Web of Science over the last 10 years were performed to identify the relevant scientific publications, on the association between alcohol consumption and metabolic syndrome. The used keywords included ‘alcohol consumption’, ‘metabolic syndrome’, ‘epidemiological study’, from ‘2004’ to ‘2015’. Of total 89 relevant publications were identified on the relation between alcohol consumption and the prevalence of metabolic syndrome (MetS) and components of MetS, 30 studies were finally included in the literature review after excluding those did not consider alcohol consumption as a primary exposure or metabolic syndrome as a primary outcome but just a result of post-hoc analyses (Appendix 1.B. Table 1-8 to Table 1-13).

1.4. Appendix 1.B. Additional Tables

Table 1-8: Alcohol consumption and the risk of metabolic syndrome, summary of studies

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Cross-sectional Studies								
Rosell et at. [165] Stockholm County, Sweden, 2003	N=4,232, age 60 only, 52% F	Low drinker Non-drinker (men) Moderate wine (men) Non-drinker (women) Moderate wine (women)	1.00 0.79 0.75 1.23 0.60	 0.41-1.51 0.48-1.20 0.80-1.89 0.40-0.91	Smoking, education, immigration, employment, physical activity, and intake of vegetables	Metabolic syndrome (EGIR: European Group for Study of Insulin Resistance, Balkau et al, 1999) [166]	- Adjustments for types of alcoholic beverages	- Elderly only - Unable to investigate cause-and-effect relationships
Djousse et al. [124] USA, 2004	N=4,510, Age 25-91, mean 51.6 ± 13.7, 54% F	Never drinkers Former drinkers (men) Current drinkers (men) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d Former drinkers (women)	1.00 1.12 0.68 0.72 0.66 0.80 0.86	 0.85-1.49 0.69-1.09 0.36-1.28 0.50-1.03 0.44-0.99 0.55-1.16	Age, education, smoking, physical activity, diabetes mellitus, coronary heart diseases, energy intake, energy from fat, fruits, vegetables, dietary	Metabolic syndrome (NCEP/ATP)	- Adjustments for types of alcoholic beverages	- Adults only - Unable to investigate cause-and-effect relationships

Author	**Sample**	**Alcohol consumption status**	**OR/RR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
		Current drinkers (women)			cholesterol, dietary			
		0.1-2.5 g/d	0.80	0.43-1.34	fibre, use of			
		2.6-12.0 g/d	0.47	0.33-0.66	multivitamins			
		12.1-24.0 g/d	0.47	0.30-0.74				
		>24.0 g/d	0.39	0.21-0.74				
		Wine (>7 drinks/w)	0.32	0.14-0.73				
		Beer (>7 drinks/w)	0.42	0.23-0.77				
		Spirits (>7 drinks/w)	0.57	0.30-1.09				
		>1 type (>7 drinks/w)	0.56	0.36-0.88				
Freiberg et al. [125] USA, 2004	N=8,125, Age >20, mean 42.7 ± 0.5 (men), 45.2 ± 0.6 (women), 52% F	< 1 (drinks/month)	1.00		Age, sex, race/ethnicity, income, tobacco use, physical activity, diet	Metabolic syndrome (NCEP/ATP)	- Large sample size - Evaluation of both type and quantity of alcohol consumed - Assessment of effect modification by race/ethnicity - Adjustments for wine, beer and spirits.	- Self-reported data with the possibility of misclassification (e.g. under reporting) - Small number of individuals in the heavy drinkers group limits ability to comment on the relation in this one
		1-19 (drinks/month)	0.65	0.54-0.79				
		≥20 (drinks/month)	0.34	0.26-0.47				
		Beer 1-19 (drinks/month)	0.75	0.61-0.91				
		Beer ≥20 (drinks/month)	0.31	0.18-0.53				
		Wine 1-19 (drinks/month)	0.64	0.51-0.79				
		Wine ≥20 (drinks/month)	0.28	0.15-0.54				
		Liquor 1-19 (drinks/month)	0.95	0.73-1.20				
		Liquor ≥20 (drinks/month)	0.74	0.49-1.14				

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Yoon et al. [137] Korea, 2004	N=7,962, Age mean 44.2 ± 14.8 (men), 45.1 ± 16.0 (women), 55% F	Non-drinkers	1.00		Sex, age, marital status, education level, smoking status, exercise, household income, waist circumference, BMI, energy intake	Metabolic syndrome (NCEP/ATP, 1998 WHO Asian Pacific Guideline)		- Ex-drinkers included in the non-drinkers group. - No adjustments for specific types of alcoholic beverages - Recall bias due to self-reported interview
		Drinkers (men)						
		1-14.9 g/d	0.71	0.53-0.95				
		15-29.9 g/d	0.88	0.63-1.24				
		30-79.9 g/d	0.87	0.63-1.19				
		≥80 g/d	1.07	0.71-1.63				
		Drinkers (women)						
		1-14.9 g/d	0.80	0.65-0.98				
		15-29.9 g/d	0.86	0.53-1.40				
		≥30 g/d	1.55	0.77-3.13				
Fan et al. [129] USA, 2005	N=2,818, Age 35-80, mean 55.4 ± 11.1, 59% F, 93% white	Drinking intensity in quartiles (drinks/drinking day)			Age, race, family history of coronary heart disease and diabetes, years of education, lifetime cigarette pack-years, current smoking and drinking status, quartiles of lifetime and current physical activity, total energy	Metabolic syndrome (NCEP ATP III)	- Among few studies investigating lifetime drinking patterns and differentiating cardiovascular risk - Measure drinking intensity (drinks or grams/day) along with average consumption (like most of studies)	- Middle ages & elderly only - Only recent measures for dietary factors (12-24 months prior to interview) - Other residual confounding was possibly failed to be included - Uncertain reports by elderly people (>80) - Other drinking patterns such as drinking with meals
		Q1	1.00					
		Q2	1.23	0.91-1.67				
		Q3	1.43	1.06-1.91				
		Q4	1.60	1.12-2.30				
		Drinking frequency in quartiles (in days)						
		Q1	1.00					
		Q2	1.07	0.80-1.42				

Author	**Sample**	**Alcohol consumption status**	**OR/RR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
		Q3	0.86	0.63-1.17	intake, percentage of energy intake from saturated fat, and dietary fiber intake		- Adjusting for a range of potential confounders	and beverage preference were not included in the analysis
		Q4	0.92	0.66-1.27				
Santos et al. [138] UK, 2007	N=2,164 Age 18-92, old, 62% F	Ethanol intake (men)			Sex, age, education, total physical activity, smoking	Metabolic syndrome (NCEP ATP III)	Measure drinking intensity (drinks or grams/day) along with average consumption (like most of studies)	- Excluding 48 older participants (≥65 years old) from analysis due to cognitive impairment may lead to selection bias - Not adjusting for dietary intake
		0 g/d	1.00					
		<10 g/d	0.85	0.37-1.96				
		10-29 g/d	0.93	0.45-1.93				
		≥30 g/d	1.56	0.82-2.96				
		Ethanol intake (women)						
		0 g/d	1.00					
		<10 g/d	1.16	0.82-1.64				
		10-29 g/d	1.22	0.85-1.76				
		≥30 g/d	1.79	0.91-3.51				
Fan et al. [130] USA, 2008	N=1,529, age 20-84	Drink exceed US guideline (>1 drink/drinking day for women and >2 drinks/drinking day for men)	1.60	1.22-2.11	Demographics, family history of cardiovascular disease and diabetes, and lifestyle factors	Metabolic syndrome (NCEP ATP III)		
		≥1 binge drinking/week	1.51	1.01-2.29				

Author	**Sample**	**Alcohol consumption status**	**OR/RR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Fan et al. [126] China, 2008	N=3,953, age 20-88, 68% F	Non-drinkers Light (1-9.9 g/d) Moderate (10-29.9 g/d) Excessive (≥30 g/d)	1.00 1.07 0.93 0.83		Demographics, BMI	Metabolic syndrome (NCEP ATP III)	- Large sample size	- Possibility of misclassification of exposure (e.g. under reporting) due to self-report - Non reporting of relative ratios and 95% CI - Not adjusting for a range of potential confounders such as smoking, physical activity, type of beverages in multivariable regression analysis
Takeuchi et al. [112] Japan, 2009	N=1,215, age 20-67, mean 42.5 ± 10.3, 100% M	Drinking Smoking and drinking	0.9 1.2	0.6-1.5 0.8-1.7	Age, previous coronary artery disease, exercise, insomnia, and stress perception	Metabolic syndrome (defined according to the International Diabetes Federation criteria (IDF))	- Measure interaction between smoking and alcohol intake	- Men only - Self-rated alcohol consumption may lead to underreporting - Number of subjects was relatively small - Not adjusting for smoking, dietary intake

Author	**Sample**	**Alcohol consumption status**	**OR/RR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Clerc et al. [139] Switzerland, 2010	N=6,172 aged 35-75 years	0 drink/week 1-13 drinks/week 14-34 drinks/week ≥35 drinks/week	1.00 0.79 0.83 1.21		Age, gender, smoking status, physical activity and education level	Metabolic syndrome (NCEP ATP III)	- AC objectively confirmed by laboratory tests (blood levels of γ-glutamyl transþrase (γGT) and carbohydrate-deficient transferrin - Large population-based sample	- Middle age and elderly only - Not reporting relative ratios (ORs) and 95% CI - Possibility misclassification of high-risk drinkers as low-risk drinkers - Not capturing drinking patterns, such as binge drinking or specific food parameters - Low proportion of beer and spirits use limited the comparison of beverage types
Kahl et al. [131] Germany, 2010	N=197, 33% F	Alcohol dependence Alcohol dependence (men) Alcohol dependence (women)	1.80 1.51 2.19		Age and sex-standardized according to the German population 2004	Metabolic syndrome (American Heart Association/National Heart, Lung and Blood Institute –	- Among few studies investigating alcohol dependence and MetS	- Carry-over effects of alcohol withdrawal - Not reporting relative ratios (ORs) and 95% CI - Insufficient or no information about eating habits and educational level

Author	**Sample**	**Alcohol consumption status**	**OR/RR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
						AHA/NHBLI 2004 criteria)		
Nakashita et al. [116] Japan, 2010	N=3,904, age ≥ 20, 100% M	Non-drinkers 0.1-22.9 g/d 23-45.9 g/d 46-69 g/d ≥69 g/d Neither smoked nor drank Non-smokers & 0.1-68.9 g/d Non-smokers & ≥69 g/d 1-29 cigars/d & non-drinkers 1-29 cigars/d & 0.1-68.9 g/d 1-29 cigars/d & ≥69 g/d ≥30 cigars/d & non-drinkers ≥30 cigars/d & 0.1-68.9 g/d	1.00 1.01 1.05 1.11 1.54 1.00 1.00 1.10 1.22 1.00 1.12 2.14 1.97 3.63	 0.77-1.33 0.79-1.40 0.79-1.54 1.06-2.23 0.67-1.48 0.36-3.37 0.72-2.08 0.67-1.49 0.55-2.26 1.05-4.36 1.23-3.16 1.91-6.90	Age, eating habits, regular exercise, and smoking	Metabolic syndrome (Japanese criteria for men)	- Investigated and showed both independent and combination relationship of cigarette smoking and alcohol consumption with MetS	- Men only - Possibility of recall bias, particularly concerning of the number of cigarettes smoked in ex-smokers and alcohol consumption in ex-drinkers

Author	**Sample**	**Alcohol consumption status**	**OR/RR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
		≥30 cigars/d & ≥69 g/d						
Wakabayashi et al. [113] Japan, 2010	N=30,585, age 30-54, 37% F	Non-drinkers (men) Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d) Non-drinkers (women) Light (<22 g/d) Heavy (≥22 g/d)	1.00 0.65 0.84 1.14 1.00 0.48 0.77	 0.57-0.75 0.76-0.92 1.03-1.27 0.25-0.90 0.49-1.19	Age, history of smoking	Metabolic syndrome (according to Japanese Committee for the Diagnostic Criteria)		- Middle ages only - Not adjusting for nutrition, food intake, physical activity, drinking pattern, and the type of alcohol beverage - Data on the polymorphism of aldehyde dehydrogenase were not available to investigate gene-alcohol interactions
Kim et al. [132] Korea, 2011	N=714, age 40-59, 100% M	Alcohol use behaviours (using AUDIT by WHO) Normal Hazardous Problem	 1.00 2.16 2.54	 1.24-3.77 1.41-4.58	Education, smoking, physical activity	Metabolic syndrome (NCEP ATP III & Western Pacific Region's Asian Pacific Guideline)	- Among few studies investigating alcohol use behaviours using AUDIT and MetS - From a large pool of population-based data	- Men & middle ages only - Unable to subdivide the alcohol use behaviours of the normal group, making it impossible to examine the association between light alcohol use and MetS and MetS components

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								- Missing data limited the generalizability of the study findings - Selection bias due to the exclusion of subjects with missing value
Wakabayashi et al. [140] Japan, 2011	N=1,960, age 30-69, 100% M with diabetes	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.91 1.08 1.46	 0.66-1.26 0.86-1.37 1.10-1.94	Age, history of smoking	Metabolic syndrome (NCEP ATP III)	- Among few studies investigating alcohol consumption among people with diabetes and MetS	- Men & middle ages only - Possibility of misdiagnosis of diabetes due to different definitions of patients with diabetes - Information of type of diabetes was not available - Information of diet, nutrition, physical activity, socioeconomic status were not available
Wakabayashi et al. [141] Japan, 2011	N=7,250, age 35-65, 100% M with	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.84 1.01 1.23	 0.71-0.98 0.90-1.13 1.08-1.40	Age, history of smoking	Metabolic syndrome (NCEP ATP III)	- Among few studies investigating alcohol consumption among people with	- Men & middle ages only - Information of type of alcohol beverages, diet, physical activity,

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
	overweight and obesity						overweight and obesity and MetS	socioeconomic status and race/ethnicity were not available
Hamaguchi et al. [114] Japan, 2012	N=18,571, age 18-88, mean 46.5 ± 9.9, 41% F	MetS - ATP III (men) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers MetS - ATP III (women) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers	 1.00 0.98 0.88 1.18 1.13 1.00 0.48 0.90 0.96 0.52	 0.83-1.15 0.75-1.04 1.01-1.39 0.67-1.90 0.27-0.82 0.50-1.65 0.37-2.48 0.24-1.15	Age, regular exercise, smoking, usage of drugs	Metabolic syndrome (NCEP ATP III & the new International Diabetes Federation (IDF) definition)	- Among few studies investigating alcohol consumption and MetS and fatty liver at the same time	- Self-reported information of alcohol intake may be underreporting - Generalizability to non-Japanese populations is uncertain - Not adjusting for dietary intakes
Wakabayashi et al. [133] Japan, 2014	N=31,295, age 35-60, 100% M	Non-drinkers Occasional heavy drinkers Regular heavy drinkers	1.00 1.94 1.48	 1.54-2.45 1.19-1.84	Age, smoking, and regular exercise as other explanatory variables	Metabolic syndrome (NCEP ATP III & IDF)	- A unique finding of this study is that the positive association	- Men and middle ages only - Information on diet, nutrition, and socioeconomic factors were not available

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							between alcohol and MetS was stronger in occasional heavy drinkers than in regular heavy drinkers, and thus, risk of MetS was suggested to be higher in the former group than in the latter group	- Detailed information on the kind of alcohol beverage was also not available - Possibilities of differences in the relationships between heavy alcohol drinking and MetS by age, gender, and race/ethnicity - Unable to investigate cause-and-effect relationships
Hirakawa et al. [142] Japan, 2015	N=22,349, age 18-95, mean 48.6±10.2, 100% M	MetS – ATP III Non-drinkers Light (<20 g/d) Heavy (≥20, <60 g/d) Very heavy (≥60 g/d) MetS – IDF Non-drinkers Light (<20 g/d)	 1.00 0.84 1.05 1.91 1.00			Metabolic syndrome (NCEP ATP III & IDF & Japanese Committee for the Diagnostic Criteria of MetS)	- Attempt different definition of MetS (both international and adapted versions for Asian participants)	- Men only - Non-drinkers included ex-drinkers - Not adjusting for a range of potential confounders such as smoking, physical activity, dietary intakes

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Heavy (≥20, <60 g/d)	0.72					- Not reporting relative ratios and 95% CIs
		Very heavy (≥60 g/d)	1.10					
		MetS – Japanese criteria	1.35					
		Non-drinkers						
		Light (<20 g/d)	1.00					
		Heavy (≥20, <60 g/d)	0.76					
		Very heavy (≥60 g/d)	1.18					
			1.40					
Cohort Studies								
Gigleux et al. [127] Canada, 2006	N=1,966 100% men, age 46-76	Alcohol consumption by quartile			Age, BMI, systolic pressure, smoking habits, type 2 diabetes (presence or not), medication for hypertension (presence or absence)	Metabolic syndrome (NCEP ATP III)	- Prospective nature of the study	- Men & middle ages only - Possible misclassification of alcohol intake due to self-report of intakes and change during follow-up - Drinking patterns were not evaluated - Not adjusting for physical activity as confounders
		<1 g/d	1.00					
		1.3-5.4 g/d	0.72	0.55-0.95				
		5.5-15.1 g/d	0.67	0.52-0.89				
		≥15.2 g/d	0.57	0.43-0.75				
Baik et al. [134]	N=3,833, age 40-69	Non-drinkers	1.00		Age, sex, BMI, income, occupation, marital status,	Metabolic syndrome (NCEP ATP III)	- Prospective nature of the study	- Middle ages only
		Very light (0.1-5 g/d)	1.06	0.71-1.58				
		Light (5.1-15 g/d)	1.13	0.69-1.83				

Author	**Sample**	**Alcohol consumption status**	**OR/RR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Korea, 2008		Moderate (15.1-30 g/d) Heavy (>30 g/d)	1.25 1.63	0.75-2.09 1.02-2.62	education, smoking status, quartiles of physical activity, energy intake, fat intake, dietary fiber intake, red meat intake, fish intake, nut intake, family history of diabetes, and family history of hypertension		- A broad range of potential confounding factors were included in the analysis	- Drinkers are likely to underreport alcohol consumption - Problem drinkers are less likely to participate in the study that may lead to selection bias - Limited data for beverage-specific drinkers
Buja et al. [135] Italy, 2010	N=1,321, Age 65-84, 100% M	At baseline (women) Abstainers <12 g/d 12-24 g/d ≥24 g/d At baseline (men) Abstainers <12 g/d 12-24 g/d	 1.00 1.01 1.12 1.10 1.00 0.93 0.98	 0.72-1.41 0.74-1.71 0.59-2.04 0.54-1.65 0.57-1.69	Age, smoking, education, consumption of vegetables, olive oil, cheese and cured meats, and anti-lipid, anti-diabetic and/or anti-hypertension therapy	Metabolic syndrome (NCEP ATP III)	- Prospective nature part of the study - Draw from a large population-based sample	- Elderly only - Lack of information on the drinking patterns - Self-reporting of alcohol use - Small sample size of the incidence phase - Not adjusting for type of alcohol beverages

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		25-47 g/d	0.76	0.43-1.36				
		≥48 g/d	1.19	0.63-2.25				
		At follow-up (women)						
		Abstainers	1.00					
		<12 g/d	1.78	1.01-2.69				
		12-24 g/d	1.31	0.60-2.43				
		≥24 g/d	1.35	0.47-2.92				
		At follow-up (men)						
		Abstainers	1.00					
		<12 g/d	2.61	0.57-7.83				
		12-24 g/d	1.56	0.32-5.73				
		25-47 g/d	2.52	0.53-7.81				
		≥48 g/d	1.12	0.16-5.55				
Kim et al. [136] Korea, 2012	N=4,505, age 23-81, 100% M	Alcohol consumption status at baseline			Age, baseline weight, lifestyle (diet, smoking, and exercise), and each component of MetS at baseline, LDL-C, hsCRP, ALT, uric	Metabolic syndrome (WHO Western Pacific Region guideline)	- Prospective nature - Analysed the effects of changes in alcohol consumption during a follow-up period, as well as the status of	- Men only - Not fully representative of general population because most subjects were urban residents - Possibility of underreporting of alcohol use
		Non-drinkers	1.00					
		Light (1.0-14.9 g/d)	1.51	1.06-2.13				
		Moderate (15.0-29.9 g/d)	1.71	1.14-2.55				
		Heavy (≥30 g/d)	2.11	1.25-3.56				
		≤1 time/month	1.00					
			1.39	0.95-2.03				

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		2-3 times/month	1.66	1.16-2.38	acid, and HOMA-IR		baseline alcohol	due to self-reported
		1-2 times/week	1.53	0.96-2.43	values		consumption, on the	information
		3-4 times/week	2.77	1.31-5.84			incidence of MetS	- Unable to analyse the
		Daily	1.00				and	effects of beverage type
		<28.25 g/time	1.20	0.90-1.59			each component of	- Lack information of
		28.25-56.4 g/time	1.31	0.94-1.84			MetS	smoking and dietary factors
		56.5-112.9 g/time	1.55	0.94-2.55			- Comprehensive	- Changed alcohol
		>113.0 g/time					measure of alcohol	consumption status might be
		Alcohol consumption					consumption status,	misclassified because alcohol
		change between baseline					in both frequency	consumption status and MetS
		& follow-up	1.00				and quantity	were assessed only at
		Non-drinkers	0.79	0.38-1.61			consumed per time	baseline and at the end of the
		New drinkers	1.46	0.75-2.82				3-year follow-up
		Ex-drinkers	1.47	0.99-2.19				
		Continuous drinkers	1.40	0.93-2.10				
		Light	1.72	1.10-2.68				
		Moderate	1.76	1.04-2.99				
		Heavy						
Shuval et al. [77] USA, 2012	N=3,411, age mean	Non-drinkers	1.00		Age, examination	Metabolic	- Prospective nature	- Men only
		Light (≤3 drinks/w)	1.51	0.97-2.36	year, smoking status,	syndrome	- Among few studies	- Limit ability to generalise
			1.66	1.11-2.48	family history of		investigating joint	findings due to selection bias

Author	**Sample**	**Alcohol consumption status**	**OR/RR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
	42.3 ± 8.6, 100% M	Moderate (>3-14 drinks/w) Heavy (>14 drinks/w)	1.29	0.90-1.85	CVD, BMI, and cardiorespiratory fitness		effect of alcohol consumption & cardiorespiratory fitness and MetS	of mostly white & well-educated participants - Quantity of alcohol intake, drinking patterns (e.g. binge drinking) were not assessed - Non-drinkers included both current and lifetime abstainers who may have differ cardio-metabolic risks - Lack of dietary information
Stoutenberg et al. [128] USA, 2013	N=7,483, age 20-100, mean 43.4 ± 9.0, 100% men	Non-drinkers Light (1-3 drinks/w) Moderate (4-7 drinks/w) Moderate-heavy (8-13 drinks/w) Heavy (14+ drinks/w)	1.00 0.81 0.68 0.70 0.78	 0.68-0.95 0.57-0.80 0.59-0.83 0.66-0.91	Age, year of examination, smoking, maximal treadmill time (min)	Metabolic syndrome (NCEP ATP III)	- Comprehensive physical examination and an extensive follow-up period in one of the largest cohort studies - Ability to stratify and adjust our models using cardiorespiratory	- Participants are males only - Limited external validity beyond Caucasian males of a higher socio-economic status - Possibility of under-reporting and subsequent misclassification of alcohol consumption - Potential

Author	Sample	Alcohol consumption status	OR/RR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							fitness rather than self-reported physical activity - One of the first prospective studies examining the relationship between AC and MetS in a US male population	misclassification of the reference group as former drinkers and lifetime abstainers have very different alcohol consumption histories - In the stratified analyses, the relatively small number of incident MetS cases in the older, normal-weight (BMI , 25 kg/m2), healthy and least fit groups may have affected the results in these groups

Table 1-9. Alcohol consumption and the risk of obesity, summary of studies

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Cross-sectional Studies								
Djousse et al. [124] USA, 2004	N=4,510, Age (mean 51.6 ± 13.7, range: 25-91), all white, 54% F	Never drinkers Former drinkers (men) Current drinkers (men) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d Former drinkers (women) Current drinkers (women) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d	1.0 1.19 0.87 0.93 0.80 0.97 1.09 0.88 0.62 0.67 1.01	 0.90-1.59 0.85-1.41 0.47-1.59 0.64-1.35 0.54-1.19 0.66-1.43 0.52-1.48 0.44-0.87 0.45-0.99 0.60-1.74	Age, age squared, sex, center, risk group (random versus high risk for CHD), current smoking, education, physical activity, and fruit and vegetable intake	Obesity	- Adjustments for a range of potential confounders	- Unable to investigate cause-and-effect relationships - Not adjusting for types of alcoholic beverages
Freiberg et al. [125] USA, 2004	N=8,125, Age >20, mean 42.7 ± 0.5 (men), 45.2 ± 0.6	< 1 (drinks/month) 1-19 (drinks/month) ≥20 (drinks/month)	1.00 0.74 0.41	 0.62-0.89 0.32-0.52	Age, sex, race/ethnicity, income, tobacco use, physical activity, diet	Large waist circumference (>102 cm in men or >88cm in women)	- Large sample size - Assessment of effect modification by race/ethnicity	- Not adjusting for types of alcoholic beverages

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
	(women), 52% F							
Yoon et al. [137] Korea, 2004	N=7,962 Age mean 44.2 ± 14.8 (men), 45.1 ± 16.0 (women), 55% F	Non-drinkers Drinkers (men) 1-14.9 g/d 15-29.9 g/d 30-79.9 g/d ≥80 g/d Drinkers (women) 1-14.9 g/d 15-29.9 g/d ≥30 g/d	1.00 0.83 0.79 1.08 2.02 1.09 1.29 1.72	 0.58-1.17 0.52-1.20 0.74-1.59 1.22-3.34 0.87-1.36 0.76-2.21 0.75-3.98	Sex, age, marital status, education level, smoking status, exercise, household income, waist circumference, BMI, energy intake	Large waist		- Ex-drinkers included in the non-drinkers group. - No adjustments for specific types of alcoholic beverages - Recall bias due to self-reported interview
Fan et al. [129] USA, 2005	N=2,818, Age 35-80, mean 55.4 ± 11.1, 59% F, 93% white	Drinking intensity in quartiles (drinks/drinking day) (women) Q1 Q2 Q3 Q4	 1.00 0.99 1.29 2.06	 0.67-1.47 0.93-1.80 1.36-3.12	Age, race, family history of coronary heart disease and diabetes, years of education, lifetime cigarette pack-years, current smoking and drinking status,	Abdominal obesity (NCEP ATP III)	- Among few studies investigating lifetime drinking patterns and differentiating cardiovascular risk - Measure drinking intensity (drinks or grams/day) along with average	- Middle ages & elderly only - Only recent measures for dietary factors (12-24 months prior to interview) - Other residual confounding was possibly failed to be included - Uncertain reports by elderly people (>80)

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Drinking frequency in quartiles (in days) (women)	1.00		quartiles of lifetime and current physical activity, total energy intake, percentage of energy intake from saturated fat, and dietary fiber intake		consumption (like most of studies) - Adjusting for a range of potential confounders	- Other drinking patterns such as drinking with meals and beverage preference were not included in the analysis
			0.79	0.56-1.11				
			0.47	0.33-0.68				
		Q1	0.42	0.29-0.62				
		Q2						
		Q3						
		Q4						
		Drinking intensity in quartiles (drinks/drinking day) (men)	1.00					
			1.54	1.00-2.38				
			1.52	0.88-2.62				
		Q1	1.87	0.92-3.81				
		Q2						
		Q3						
		Q4						
		Drinking frequency in quartiles (in days) (men)	1.00					
			0.85	0.55-1.31				
		Q1	0.82	0.53-1.27				
		Q2	0.78	0.50-1.22				
		Q3						
		Q4						

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Fan et al. [126] China, 2008	N=3,953, age 20-88, 68% F	Non-drinkers Light (1-9.9 g/d) Moderate (10-29.9 g/d) Excessive (≥30 g/d)	1.00 1.01 0.66 0.64		Demographics, BMI	ABO: WHO criteria for Asians	- Large sample size	- Non reporting of relative ratios and 95% CI - Not adjusting for a range of potential confounders such as smoking, physical activity, type of beverages in multivariable regression analysis
Takeuchi et al. [112] Japan, 2009	N=1,215, age 20-67, mean 42.5 ± 10.3, 100% M	Drinking Smoking and drinking	1.0 1.3	0.7-1.4 1.0-1.7	Age, previous coronary artery disease, exercise, insomnia, and stress perception	Large waist circumference using Japanese-specific value (≥90 cm) of the IDF	- Measure interaction between smoking and alcohol intake	- Men only - Self-rated alcohol consumption may lead to underreporting - Number of subjects was relatively small - Not adjusting for smoking, dietary intake
Kahl et al. [131] Germany, 2010	N=197, age ≥18, 33% F	Alcohol dependence Alcohol dependence (men) Alcohol dependence (women)	1.04 0.79 1.25		Age and sex-standardized according to the German population 2004	Large waist circumference (>102 cm in men or >88cm in women)	- Among few studies investigating alcohol dependence and MetS	- Carry-over effects of alcohol withdrawal - Not reporting relative ratios (ORs) and 95% CI

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								- Insufficient or no information about eating habits and educational level
Nakashita et al. [116] Japan, 2010	N=3,904, age ≥ 20, 100% M	Non-drinkers 0.1-22.9 g/d 23-45.9 g/d 46-69 g/d ≥69 g/d	1.00 0.99 1.13 1.21 1.54	 0.82-1.20 0.92-1.39 0.94-1.54 1.15-2.05	Age, eating habits, regular exercise, and smoking	Large waist circumference (≥85 cm)		- Men only
Wakabayashi et al. [113] Japan, 2010	N=30,585, age 30-54, 37% F	Non-drinkers (men) Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d) Non-drinkers (women) Light (<22 g/d) Heavy (≥22 g/d)	1.00 0.72 0.82 1.00 1.00 0.64 0.70	 0.65-0.79 0.76-0.88 0.92-1.08 0.47-0.86 0.55-0.89	Age, history of smoking	Large waist circumference (≥85 cm for men and ≥ 90 cm for women)		- Middle ages only - Not adjusting for nutrition, food intake, physical activity, drinking pattern, and the type of alcohol beverage - Data on the polymorphism of aldehyde dehydrogenase were not available to investigate gene-alcohol interactions
Kim et al. [132]	N=714, age 40-59, 100% M	Alcohol use behaviours (using AUDIT by WHO) Normal	 1.00		Education, smoking, physical activity	Large waist circumference (> 90 cm)	- Among few studies investigating alcohol	- Men & middle ages only

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Korea, 2011		Hazardous Problem	1.93 1.85	1.17-3.19 1.17-2.92			use behaviours using AUDIT - From a large pool of population-based data	- Impossible to examine the effects of light alcohol use on MetS components - Missing data limited the generalizability of the study findings - Selection bias due to the exclusion of subjects with missing value
Wakabayashi et al. [140] Japan, 2011	N=1,960, age 30-69, 100% M with diabetes	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.95 0.95 1.02	 0.69-1.31 0.75-1.19 0.79-1.33	Age, history of smoking	Large waist circumference (≥85 cm)	- Among few studies investigating alcohol consumption among people with diabetes and MetS	- Men and middle ages only - Information of type of diabetes was not available - Information of diet, nutrition, physical activity, socioeconomic status were not available
Wakabayashi et al. [141] Japan, 2011	N=7,250, age 35-65, 100% M with	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.87 1.14 1.14	 0.66-1.13 0.93-1.39 0.90-1.43	Age, history of smoking	Large waist circumference (≥85 cm)	- Among few studies investigating alcohol consumption among people with	- Men & middle ages only - Information of type of alcohol beverages, diet, physical activity, socioeconomic status and

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
	overweight and obesity						overweight and obesity and MetS	race/ethnicity were not available
Hamaguchi et al. [114] Japan, 2012	N=18,571, age 18-88, mean 46.5 ± 9.9, 41% F	MetS - ATP III (men) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers MetS - ATP III (women) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers	 1.00 0.96 0.89 1.06 0.63 1.00 0.71 0.57 1.06 0.68	 0.81-1.13 0.75-1.06 0.89-1.27 0.32-1.23 0.51-0.97 0.36-0.90 0.58-1.93 0.43-1.07	Age, regular exercise, smoking, usage of drugs	Large waist circumference (≥90 cm for men and ≥ 80 cm for women)	- Among few studies investigating alcohol consumption and MetS and fatty liver at the same time	- Self-reported information of alcohol intake may be underreporting - Generalizability to non-Japanese populations is uncertain - Not adjusting for dietary intakes
Wakabayashi et al. [133] Japan, 2014	N=31,295, age 35-60, 100% M	Non-drinkers Occasional heavy drinkers Regular heavy drinkers	1.00 1.96 1.12	 1.63-2.35 0.96-1.32	Age, smoking, and regular exercise as other explanatory variables	Large waist circumference	- A unique finding of this study is that the positive association	- Men and middle ages only - Information on diet, nutrition, and socioeconomic factors were not available - Detailed information

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							between alcohol and MetS was stronger in occasional heavy drinkers than in regular heavy drinkers, and thus, risk of MetS was suggested to be higher in the former group than in the latter group	on the kind of alcohol beverage was also not available - Possibilities of differences in the relationships between heavy alcohol drinking and MetS by age, gender, and race/ethnicity - Unable to investigate cause-and-effect relationships
Hirakawa et al. [142] Japan, 2015	N=22,349, age 18-95, mean 48.6±10.2, 100% M	Waist – ATP III (>102 cm) Non-drinkers Light (<20 g/d) Heavy (≥20, <60 g/d) Very heavy (≥60 g/d) Waist – IDF (≥90 cm) Non-drinkers Light (<20 g/d)	 1.00 0.60 0.65 1.20 1.00 0.84 1.08			Waist >102 cm (NCEP ATP III) Waist ≥90 cm or BMI >30 kg/m^2 (IDF) Waist ≥85 cm (Japanese criteria of MetS)	- Attempt different definition of MetS (both international and adapted versions for Asian participants)	- Men only - Non-drinkers included ex-drinkers - Not adjusting for a range of potential confounders such as smoking, physical activity, dietary intakes - Not reporting relative ratios and 95% CIs

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Heavy (≥20, <60 g/d)	1.32					
		Very heavy (≥60 g/d)						
		Waist – Japanese (≥85	1.00					
		cm)	0.87					
		Non-drinkers	1.02					
		Light (<20 g/d)	1.12					
		Heavy (≥20, <60 g/d)						
		Very heavy (≥60 g/d)						
Cohort Studies								
Gigleux et al. [127] Canada, 2006	N=1,966 100% men, age 46-76	Alcohol consumption by quartile			Age, smoking habits, type 2 diabetes (presence or not), medication for hypertension (presence or absence)	BMI (>30 kg/m^2)	- Prospective nature of the study	- Possible misclassification of alcohol intake due to self-report of intakes and change during follow-up - Drinking patterns were not evaluated - Not adjusting for physical activity as confounders
		<1 g/d	1.00					
		1.3-5.4 g/d	0.81	0.56-1.16				
		5.5-15.1 g/d	0.69	0.50-1.00				
		≥15.2 g/d	0.69	0.48-1.01				
Baik et al. [134] Korea, 2008	N=3,833, age 40-69	Non-drinkers	1.00		Age, sex, BMI, income, occupation, marital status,	Large waist circumference (>102 cm for men	- Prospective nature of the study - A broad range of potential	- Middle ages only - Limited data for beverage-specific drinkers
		Very light (0.1-5 g/d)	1.84	1.08-3.14				
		Light (5.1-15 g/d)	1.43	0.57-3.58				
		Moderate (15.1-30 g/d)	1.10	0.30-4.01				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Heavy (>30 g/d)	3.61	1.09-12.01	education, smoking status, quartiles of physical activity, energy intake, fat intake, dietary fiber intake, red meat intake, fish intake, nut intake, family history of diabetes, and family history of hypertension	or >88 cm for women)	confounding factors were included in the analysis	
Buja et al. [135] Italy, 2010	N=1,321, Age 65-84, 100% M	At baseline (women)			Age, smoking, education and consumption of fish, coffee, vegetables, olive oil, cheese and cured meats	Waist > 88 cm for women and waist > 102 cm for men	- Prospective nature part of the study - Draw from a large population-based sample	- Elderly only - Lack of information on the drinking patterns - Self-reporting of alcohol use - Small sample size of the incidence phase - Not adjusting for type of alcohol beverages
		Abstainers	1.00					
		<12 g/d	1.01	0.75-1.38				
		12-24 g/d	1.36	0.92-2.03				
		≥24 g/d	1.37	0.76-2.46				
		At baseline (men)						
		Abstainers	1.00					
		<12 g/d	0.76	0.48-1.21				
		12-24 g/d	0.95	0.61-1.48				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		25-47 g/d	1.02	0.65-1.61				
		≥48 g/d	1.29	0.79-2.10				
		At follow-up (women)						
		Abstainers	1.00					
		<12 g/d	1.53	0.73-2.74				
		12-24 g/d	1.66	0.70-3.11				
		≥24 g/d	-	-				
		At follow-up (men)						
		Abstainers	1.00					
		<12 g/d	2.12	0.47-7.89				
		12-24 g/d	1.78	0.40-6.70				
		25-47 g/d	1.99	0.44-7.49				
		≥48 g/d	2.30	0.49-8.55				
Kim et al. [136] Korea, 2012	N=4,505, age 23-81, 100% M	Alcohol consumption status at baseline			Age, baseline weight, lifestyle (diet, smoking, and exercise), and each component of MetS at baseline, LDL-C, hsCRP, ALT, uric	Abdominal obesity (waist circumference >90 cm or BMI ≥25 kg/m^2)	- Prospective nature - Analysed the effects of changes in alcohol consumption during a follow-up period, as well as the status of	- Men only - Not fully representative of general population because most subjects were urban residents - Possibility of underreporting of alcohol use
		Non-drinkers	1.00					
		Light (1.0-14.9 g/d)	0.98	0.69-1.39				
		Moderate (15.0-29.9 g/d)	0.75	0.48-1.17				
		Heavy (≥30 g/d)	0.94	0.51-1.74				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
					acid, and HOMA-IR values		baseline alcohol consumption, on the incidence of MetS and each component of MetS	due to self-reported information - Unable to analyse the effects of beverage type - Lack information of smoking and dietary factors - Changed alcohol consumption status might be misclassified because alcohol consumption status and MetS were assessed only at baseline and at the end of the 3-year follow-up
Shuval et al. [77] USA, 2012	N=3,411, age mean 42.3 ± 8.6, 100% M	Non-drinkers Light (≤3 drinks/w) Moderate (>3-14 drinks/w) Heavy (>14 drinks/w)	1.00 1.20 1.50 1.19	 0.74-1.94 0.97-2.32 0.80-1.76	Age, examination year, smoking status, family history of CVD, BMI, and cardiorespiratory fitness	Elevated Waist Circumference (≥102 cm)	- Prospective nature - Among few studies investigating joint effect of alcohol consumption & cardiorespiratory fitness and MetS	- Men only - Limit ability to generalise findings due to selection bias of mostly white & well-educated participants - Quantity of alcohol intake, drinking patterns (e.g. binge drinking) were not assessed

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								- Non-drinkers included both current and lifetime abstainers who may have differ cardio-metabolic risks - Lack of dietary information
Stoutenberg et al. [128] USA, 2013	N=7,483, age 20-100, mean 43.4 ± 9.0, 100% men	Non-drinkers Light (1-3 drinks/w) Moderate (4-7 drinks/w) Moderate-heavy (8-13 drinks/w) Heavy (14+ drinks/w)	1.00 0.86 0.88 0.96 1.05	 0.65-1.13 0.67-1.14 0.74-1.26 0.81-1.35	Age, year of examination, smoking, maximal treadmill time (min)	Central obesity (waist circumference >102 cm)	- Comprehensive physical examination and an extensive follow-up period in one of the largest cohort studies - Ability to stratify and adjust our models using cardiorespiratory fitness rather than self-reported physical activity - One of the first prospective studies examining the	- Participants are males only - Limited external validity beyond Caucasian males of a higher socio-economic status - Possibility of under-reporting and subsequent misclassification of alcohol consumption - Potential misclassification of the reference group as former drinkers and lifetime abstainers have very different alcohol consumption histories

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							relationship between AC and MetS in a US male population	- In the stratified analyses, the relatively small number of incident MetS cases in the older, normal-weight (BMI , 25 kg/m2), healthy and least fit groups may have affected the results in these groups

Table 1-10: Alcohol consumption and the risk of low level of high-density lipoprotein cholesterol (Low HDL-C), summary of studies

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Cross-sectional Studies								
Djousse et al. [124] USA, 2004	N=4,510, Age (mean 51.6 ± 13.7, range: 25-91), all white, 54% F	Never drinkers Former drinkers (men) Current drinkers (men) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d Former drinkers (women) Current drinkers (women) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d	1.00 0.92 0.56 0.59 0.25 0.28 0.90 0.86 0.51 0.42 0.24	 0.70-1.20 0.31-1.01 0.41-0.84 0.16-0.38 0.19-0.41 0.72-1.13 0.53-1.40 0.37-0.70 0.27-0.64 0.12-0.47	Age, age squared, sex, center, risk group (random versus high risk for CHD), current smoking, education, physical activity, and fruit and vegetable intake	Low HDL cholesterol	- Adjustments for a range of potential confounders	- Unable to investigate cause-and-effect relationships - Not adjusting for types of alcoholic beverages
Freiberg et al. [125] USA, 2004	N=8,125, Age >20, mean 42.7 ± 0.5 (men), 45.2 ± 0.6	< 1 (drinks/month) 1-19 (drinks/month) ≥20 (drinks/month)	1.00 0.69 0.22	 0.60-0.78 0.16-0.29	Age, sex, race/ethnicity, income, tobacco use, physical activity, diet	Low serum HDL cholesterol (<1.04 mmol/l in men or <1.29 mmol/l in women)	- Large sample size - Assessment of effect modification by race/ethnicity	- Not adjusting for types of alcoholic beverages

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
	(women), 52% F							
Yoon et al. [137] Korea, 2004	N=7,962 Age mean 44.2 ± 14.8 (men), 45.1 ± 16.0 (women), 55% F	Non-drinkers Drinkers (men) 1-14.9 g/d 15-29.9 g/d 30-79.9 g/d ≥80 g/d Drinkers (women) 1-14.9 g/d 15-29.9 g/d ≥30 g/d	1.00 0.73 0.46 0.29 0.26 0.85 0.53 0.35	 0.57-0.92 0.34-0.63 0.22-0.40 0.17-0.41 0.73-0.99 0.36-0.77 0.19-0.64	Sex, age, marital status, education level, smoking status, exercise, household income, waist circumference, BMI, energy intake	Low HDL cholesterol		- Ex-drinkers included in the non-drinkers group. - No adjustments for specific types of alcoholic beverages - Recall bias due to self-reported interview
Fan et al. [129] USA, 2005	N=2,818, Age 35-80, mean 55.4 ± 11.1, 59% F, 93% white	Drinking intensity in quartiles (drinks/drinking day) Q1 Q2 Q3 Q4 Drinking frequency in quartiles (in days)	 1.00 1.51 1.03 1.32	 1.03-2.19 0.71-1.50 0.83-2.10	Age, race, family history of coronary heart disease and diabetes, years of education, lifetime cigarette pack-years, current smoking and drinking status,	Low HDL cholesterol (NCEP ATP III)	- Among few studies investigating lifetime drinking patterns and differentiating cardiovascular risk - Measure drinking intensity (drinks or grams/day) along with average	- Middle ages & elderly only - Only recent measures for dietary factors (12-24 months prior to interview) - Other residual confounding was possibly failed to be included - Uncertain reports by elderly people (>80)

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Q1 Q2 Q3 Q4	1.00 0.97 0.51 0.54	 0.68-1.37 0.34-0.75 0.36-0.81	quartiles of lifetime and current physical activity, total energy intake, percentage of energy intake from saturated fat, and dietary fiber intake		consumption (like most of studies) - Adjusting for a range of potential confounders	- Other drinking patterns such as drinking with meals and beverage preference were not included in the analysis
Fan et al. [126] China, 2008	N=3,953, age 20-88, 68% F	Non-drinkers Light (1-9.9 g/d) Moderate (10-29.9 g/d) Excessive (≥30 g/d)	1.00 0.91 0.76 0.44		Demographics, BMI	Low HDL cholesterol: NCEP ATP III	- Large sample size	- Non reporting of relative ratios and 95% CI - Not adjusting for a range of potential confounders such as smoking, physical activity, type of beverages in multivariable regression analysis
Takeuchi et al. [112] Japan, 2009	N=1,215 , age 20-67, mean 42.5 ± 10.3, 100% M	Drinking Smoking and drinking	0.4 0.9	0.3-0.7 0.6-1.4	Age, previous coronary artery disease, exercise, insomnia, and stress perception	Low HDL cholesterol: <40 mg/dL (IDF)	- Measure interaction between smoking and alcohol intake	- Men only - Self-rated alcohol consumption may lead to underreporting - Number of subjects was relatively small

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
								- Not adjusting for smoking, dietary intake
Kahl et al. [131] Germany, 2010	N=197, age ≥18, 33% F	Alcohol dependence Alcohol dependence (men) Alcohol dependence (women)	0.26 0.38 0.13		Age and sex-standardized according to the German population 2004	Low HDL cholesterol (<40 mg/dL for men or <50 mg/dL for women)	- Among few studies investigating alcohol dependence and MetS	- Carry-over effects of alcohol withdrawal - Not reporting relative ratios (ORs) and 95% CI - Insufficient or no information about eating habits and educational level
Nakashita et al. [116] Japan, 2010	N=3,904, age ≥ 20, 100% M	Non-drinkers 0.1-22.9 g/d 23-45.9 g/d 46-69 g/d ≥69 g/d	1.00 0.90 0.57 0.59 0.47	 0.70-1.18 0.42-0.77 0.41-0.85 0.29-0.74	Age, eating habits, regular exercise, and smoking	Low HDL cholesterol (<40 mg/dL or treatment for either elevated triglyceride or low HDL cholesterol)		- Men only - Possibility of misdiagnosis of low HDL-C due to different criteria
Wakabayashi et al. [113]	N=30,585, age 30-54, 37% F	Non-drinkers (men) Light (<22 g/d) Heavy (≥22, <44 g/d)	1.00 0.39 0.34	 0.33-0.47 0.30-0.39	Age, history of smoking, BMI, history of therapy for	Low HDL cholesterol (<40 mg/dL for men		- Middle ages only - Not adjusting for nutrition, food intake, physical activity,

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Japan, 2010		Very heavy (≥44 g/d) Non-drinkers (women) Light (<22 g/d) Heavy (≥22 g/d)	0.26 1.00 0.11 0.30	0.22-0.30 0.03-0.45 0.15-0.60	hypertension, dyslipidaemia or diabetes mellitus	and <50 mg/dL for women)		drinking pattern, and the type of alcohol beverage - Data on the polymorphism of aldehyde dehydrogenase were not available to investigate gene-alcohol interactions
Kim et al. [132] Korea, 2011	N=714, age 40-59, 100% M	Alcohol use behaviours (using AUDIT by WHO) Normal Hazardous Problem	 1.00 1.04 1.07	 0.52-2.07 0.54-2.13	Education, smoking, physical activity	Low HDL cholesterol (<40 mg/dL)	- Among few studies investigating alcohol use behaviours using AUDIT - From a large pool of population-based data	- Men & middle ages only - Impossible to examine the effects of light alcohol use on MetS components - Missing data limited the generalizability of the study findings - Selection bias due to the exclusion of subjects with missing value
Wakabayashi et al. [140]	N=1,960, age 30-69, 100% M	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.42 0.28 0.22	 0.28-0.65 0.20-0.39 0.15-0.34	Age, history of smoking, BMI, history of therapy for hypertension,	Low HDL cholesterol (<40 mg/dL)	- Among few studies investigating alcohol consumption among	- Men and middle ages only - Information of type of diabetes was not available

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Japan, 2011	with diabetes				dyslipidaemia or diabetes mellitus		people with diabetes and MetS	- Information of diet, nutrition, physical activity, socioeconomic status were not available
Wakabayashi et al. [141] Japan, 2011	N=7,250, age 35-65, 100% M with overweight and obesity	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.40 0.35 0.27	 0.32-0.50 0.30-0.41 0.22-0.33	Age, history of smoking, BMI, history of therapy for hypertension, dyslipidaemia or diabetes mellitus	Low HDL cholesterol (<40 mg/dL)	- Among few studies investigating alcohol consumption among people with overweight and obesity and MetS	- Men & middle ages only - Information of type of alcohol beverages, diet, physical activity, socioeconomic status and race/ethnicity were not available
Hamaguchi et al. [114] Japan, 2012	N=18,571, age 18-88, mean 46.5 ± 9.9, 41% F	MetS - ATP III (men) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers MetS - ATP III (women) Non-drinkers Light (40-140 g/w)	 1.00 0.70 0.49 0.41 0.79 1.00 0.58 0.43	 0.61-0.80 0.42-0.57 0.35-0.48 0.47-1.32 0.42-0.79 0.27-0.69	Age, regular exercise, smoking, usage of drugs	Low HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women) or on treatment	- Among few studies investigating alcohol consumption and MetS and fatty liver at the same time	- Self-reported information of alcohol intake may be underreporting - Generalizability to non-Japanese populations is uncertain - Not adjusting for dietary intakes

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers	0.48 0.90	0.24-0.96 0.60-1.35				
Wakabayashi et al. [133] Japan, 2014	N=31,295, age 35-60, 100% M	Non-drinkers Occasional heavy drinkers Regular heavy drinkers	1.00 0.52 0.16	 0.39-0.68 0.11-0.23	Age, smoking, and regular exercise as other explanatory variables	Low HDL cholesterol (<40 mg/dL)	- A unique finding of this study is that the positive association between alcohol and MetS was stronger in occasional heavy drinkers than in regular heavy drinkers, and thus, risk of MetS was suggested to be higher in the former group than in the latter group	- Men and middle ages only - Information on diet, nutrition, and socioeconomic factors were not available - Detailed information on the kind of alcohol beverage was also not available - Possibilities of differences in the relationships between heavy alcohol drinking and MetS by age, gender, and race/ethnicity - Unable to investigate cause-and-effect relationships

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Hirakawa et al. [142] Japan, 2015	N=22,349, age 18-95, mean 48.6±10.2, 100% M	Non-drinkers Light (<20 g/d) Heavy (≥20, <60 g/d) Very heavy (≥60 g/d)	1.00 0.85 0.64 0.60			Low HDL cholesterol (<40 mg/dL)	- Attempt different definition of MetS (both international and adapted versions for Asian participants)	- Men only - Non-drinkers included ex-drinkers - Not adjusting for a range of potential confounders such as smoking, physical activity, dietary intakes - Not reporting relative ratios and 95% CIs
Cohort Studies								
Gigleux et al. [127] Canada, 2006	N=1,966 100% men, age 46-76	Alcohol consumption by quartile <1 g/d 1.3-5.4 g/d 5.5-15.1 g/d ≥15.2 g/d	 1.00 0.62 0.49 0.28	 0.48-0.82 0.38-0.64 0.22-0.37	Age, smoking habits, type 2 diabetes (presence or not), medication for hypertension (presence or absence)	Low HDL cholesterol (< 1.0 mmol/l)	- Prospective nature of the study	- Possible misclassification of alcohol intake due to self-report of intakes and change during follow-up - Drinking patterns were not evaluated - Not adjusting for physical activity as confounders

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Baik et al. [134] Korea, 2008	N=3,833, age 40-69	Non-drinkers Very light (0.1-5 g/d) Light (5.1-15 g/d) Moderate (15.1-30 g/d) Heavy (>30 g/d)	1.00 0.81 0.61 0.41 0.39	 0.69-0.95 0.50-0.75 0.33-0.52 0.31-0.49	Age, sex, BMI, income, occupation, marital status, education, smoking status, quartiles of physical activity, energy intake, fat intake, dietary fiber intake, red meat intake, fish intake, nut intake, family history of diabetes, and family history of hypertension	Low HDL cholesterol (<40 mg/dL for men or <50 mg/dL for women)	- Prospective nature of the study - A broad range of potential confounding factors were included in the analysis	- Middle ages only - Limited data for beverage-specific drinkers
Buja et al. [135] Italy, 2010	N=1,321, Age 65-84, 100% M	At baseline (women) Abstainers <12 g/d 12-24 g/d ≥24 g/d At baseline (men)	 1.00 1.10 0.89 1.01	 0.80-1.52 0.59-1.33 0.55-1.86	Age, smoking, education and consumption of fish, coffee, vegetables, olive oil, cheese and cured meats	Low HDL cholesterol (<50 mg/dL for women and <40 mg/dL for men)	- Prospective nature part of the study - Draw from a large population-based sample	- Elderly only - Lack of information on the drinking patterns - Self-reporting of alcohol use

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Abstainers	1.00					- Small sample size of the incidence phase - Not adjusting for type of alcohol beverages
		<12 g/d	0.86	0.48-1.54				
		12-24 g/d	0.63	0.35-1.11				
		25-47 g/d	0.49	0.26-0.92				
		≥48 g/d	0.34	0.16-0.71				
		At follow-up (women)						
		Abstainers	1.00					
		<12 g/d	1.26	0.76-1.77				
		12-24 g/d	0.94	0.46-1.57				
		≥24 g/d	1.04	0.35-1.91				
		At follow-up (men)						
		Abstainers	1.00					
		<12 g/d	0.80	0.31-1.77				
		12-24 g/d	0.65	0.25-1.50				
		25-47 g/d	0.73	0.27-1.69				
		≥48 g/d	0.38	0.11-1.21				
Kim et al. [136] Korea, 2012	N=4,505, age 23-81, 100% M	Alcohol consumption status at baseline			Age, baseline weight, lifestyle (diet, smoking, and exercise), and each component of MetS	Low HDL cholesterol (<40 mg/dL)	- Prospective nature - Analysed the effects of changes in alcohol consumption	- Men only - Not fully representative of general population because most subjects were urban residents
		Non-drinkers	1.00					
		Light (1.0-14.9 g/d)	0.71	0.53-0.96				
			0.42	0.28-0.64				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Moderate (15.0-29.9 g/d) Heavy (≥30 g/d)	0.33	0.16-0.66	at baseline, LDL-C, hsCRP, ALT, uric acid, and HOMA-IR values		during a follow-up period, as well as the status of baseline alcohol consumption, on the incidence of MetS and each component of MetS	- Possibility of underreporting of alcohol use due to self-reported information - Unable to analyse the effects of beverage type - Lack information of smoking and dietary factors - Changed alcohol consumption status might be misclassified because alcohol consumption status and MetS were assessed only at baseline and at the end of the 3-year follow-up
Shuval et al. [77] USA, 2012	N=3,411, age mean 42.3 ± 8.6, 100% M	Non-drinkers Light (≤3 drinks/w) Moderate (>3-14 drinks/w) Heavy (>14 drinks/w)	1.00 2.38 1.69 1.17	 1.59-3.57 1.14-2.52 0.81-1.70	Age, examination year, smoking status, family history of CVD, BMI, and cardiorespiratory fitness	Low HDL cholesterol (<40 mg/dL)	- Prospective nature - Among few studies investigating joint effect of alcohol consumption &	- Men only - Limit ability to generalise findings due to selection bias of mostly white & well-educated participants

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							cardiorespiratory fitness and MetS	- Quantity of alcohol intake, drinking patterns (e.g. binge drinking) were not assessed - Non-drinkers included both current and lifetime abstainers who may have differ cardio-metabolic risks - Lack of dietary information
Stoutenberg et al. [128] USA, 2013	N=7,483, age 20-100, mean 43.4 ± 9.0, 100% men	Non-drinkers Light (1-3 drinks/w) Moderate (4-7 drinks/w) Moderate-heavy (8-13 drinks/w) Heavy (14+ drinks/w)	1.00 0.71 0.67 0.50 0.52	 0.58-0.87 0.55-0.81 0.41-0.62 0.43-0.64	Age, year of examination, smoking, maximal treadmill time (min)	Low HDL cholesterol (<4 mg/l)	- Comprehensive physical examination and an extensive follow-up period in one of the largest cohort studies - Ability to stratify and adjust our models using cardiorespiratory fitness rather than self-reported physical activity	- Participants are males only - Limited external validity beyond Caucasian males of a higher socio-economic status - Possibility of under-reporting and subsequent misclassification of alcohol consumption - Potential misclassification of the reference group as former drinkers and

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							- One of the first prospective studies examining the relationship between AC and MetS in a US male population	lifetime abstainers have very different alcohol consumption histories - In the stratified analyses, the relatively small number of incident MetS cases in the older, normal-weight (BMI , 25 kg/m2), healthy and least fit groups may have affected the results in these groups

Table 1-11. Alcohol consumption and the risk of hypertriglyceridemia (high serum triglyceride concentration), summary of studies

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Cross-sectional Studies								
Djousse et al. [124] USA, 2004	N=4,510, Age (mean 51.6 ± 13.7, range: 25-91), all white, 54% F	Never drinkers Former drinkers (men) Current drinkers (men) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d Former drinkers (women) Current drinkers (women) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d	1.00 1.14 1.33 0.83 0.86 1.18 0.84 0.85 0.57 0.49 0.61	 0.86-1.51 0.74-2.40 0.57-1.19 0.58-1.28 0.81-1.71 0.66-1.07 0.50-1.46 0.41-0.79 0.32 	Age, age squared, sex, center, risk group (random versus high risk for CHD), current smoking, education, physical activity, and fruit and vegetable intake	High triglycerides	- Adjustments for a range of potential confounders	- Unable to investigate cause-and-effect relationships - Not adjusting for types of alcoholic beverages
Freiberg et al. [125] USA, 2004	N=8,125, Age >20, mean 42.7 ± 0.5 (men), 45.2 ± 0.6	< 1 (drinks/month) 1-19 (drinks/month) ≥20 (drinks/month)	1.00 0.73 0.56	 0.62-0.87 0.43-0.74	Age, sex, race/ethnicity, income, tobacco use, physical activity, diet	High serum triglycerides (≥ 1.69 mmol/l)	- Large sample size - Assessment of effect modification by race/ethnicity	- Not adjusting for types of alcoholic beverages

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
	(women), 52% F							
Yoon et al. [137] Korea, 2004	N=7,962 Age mean 44.2 ± 14.8 (men), 45.1 ± 16.0 (women), 55% F	Non-drinkers Drinkers (men) 1-14.9 g/d 15-29.9 g/d 30-79.9 g/d ≥80 g/d Drinkers (women) 1-14.9 g/d 15-29.9 g/d ≥30 g/d	1.00 0.89 1.09 1.37 1.76 0.82 1.24 2.19	 0.71-1.14 0.83-1.44 1.05-1.77 1.23-2.50 0.68-0.99 0.71-1.90 1.21-3.97	Sex, age, marital status, education level, smoking status, exercise, household income, waist circumference, BMI, energy intake	High triglycerides		- Ex-drinkers included in the non-drinkers group. - No adjustments for specific types of alcoholic beverages - Recall bias due to self-reported interview
Fan et al. [129] USA, 2005	N=2,818, Age 35-80, mean 55.4 ± 11.1, 59% F, 93% white	Drinking intensity in quartiles (drinks/drinking day) Q1 Q2 Q3 Q4 Drinking frequency in quartiles (in days)	 1.00 1.13 1.32 1.39	 0.86-1.49 1.01-1.73 0.88-1.93	Age, race, family history of coronary heart disease and diabetes, years of education, lifetime cigarette pack-years, current smoking and drinking status,	High triglycerides (NCEP ATP III)	- Among few studies investigating lifetime drinking patterns and differentiating cardiovascular risk - Measure drinking intensity (drinks or grams/day) along with average	- Middle ages & elderly only - Only recent measures for dietary factors (12-24 months prior to interview) - Other residual confounding was possibly failed to be included - Uncertain reports by elderly people (>80)

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
		Q1 Q2 Q3 Q4	1.00 0.99 0.99 0.99	 0.75-1.32 0.73-1.33 0.75-1.33	quartiles of lifetime and current physical activity, total energy intake, percentage of energy intake from saturated fat, and dietary fiber intake		consumption (like most of studies) - Adjusting for a range of potential confounders	- Other drinking patterns such as drinking with meals and beverage preference were not included in the analysis
Fan et al. [126] China, 2008	N=3,953, age 20-88, 68% F	Non-drinkers Light (1-9.9 g/d) Moderate (10-29.9 g/d) Excessive (≥30 g/d)	1.00 1.18 1.29 1.32		Demographics, BMI	High triglycerides: NCEP ATP III	- Large sample size	- Non reporting of relative ratios and 95% CI - Not adjusting for a range of potential confounders such as smoking, physical activity, type of beverages in multivariable regression analysis
Takeuchi et al. [112] Japan, 2009	N=1,215 , age 20-67, mean 42.5 ± 10.3, 100% M	Drinking Smoking and drinking	1.0 1.8	0.7-1.3 1.4-2.3	Age, previous coronary artery disease, exercise, insomnia, and stress perception	High triglycerides: ≥150 mg/dL (IDF)	- Measure interaction between smoking and alcohol intake	- Men only - Self-rated alcohol consumption may lead to underreporting - Number of subjects was relatively small

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
								- Not adjusting for smoking, dietary intake
Kahl et al. [131] Germany, 2010	N=197, age ≥18, 33% F	Alcohol dependence Alcohol dependence (men) Alcohol dependence (women)	1.81 1.37 3.08		Age and sex-standardized according to the German population 2004	High triglycerides: ≥150 mg/dL	- Among few studies investigating alcohol dependence and MetS	- Carry-over effects of alcohol withdrawal - Not reporting relative ratios (ORs) and 95% CI - Insufficient or no information about eating habits and educational level
Nakashita et al. [116] Japan, 2010	N=3,904, age ≥ 20, 100% M	Non-drinkers 0.1-22.9 g/d 23-45.9 g/d 46-69 g/d ≥69 g/d	1.00 0.96 0.97 1.18 1.80	 0.77-1.18 0.78-1.22 0.91-1.54 1.33-2.43	Age, eating habits, regular exercise, and smoking	High triglycerides (≥150 mg/dL)		- Men only
Wakabayashi et al. [113] Japan, 2010	N=30,585, age 30-54, 37% F	Non-drinkers (men) Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d) Non-drinkers (women) Light (<22 g/d) Heavy (≥22 g/d)	1.00 0.98 1.23 1.62 1.00 0.75 1.06	 0.88-1.10 1.14-1.33 1.49-1.77 0.55-1.01 0.28-1.21	Age, history of smoking, BMI, history of therapy for hypertension, dyslipidaemia or diabetes mellitus	High triglycerides (≥150 mg/dL)		- Middle ages only - Not adjusting for nutrition, food intake, physical activity, drinking pattern, and the type of alcohol beverage - Data on the polymorphism of aldehyde dehydrogenase

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								were not available to investigate gene-alcohol interactions
Kim et al. [132] Korea, 2011	N=714, age 40-59, 100% M	Alcohol use behaviours (using AUDIT by WHO) Normal Hazardous Problem	 1.00 1.43 2.19	 0.94-2.17 1.38-3.47	Education, smoking, physical activity	High triglycerides (≥ 150 mg/dL)	- Among few studies investigating alcohol use behaviours using AUDIT - From a large pool of population-based data	- Men & middle ages only - Impossible to examine the effects of light alcohol use on MetS components - Missing data limited the generalizability of the study findings - Selection bias due to the exclusion of subjects with missing value
Wakabayashi et al. [140] Japan, 2011	N=1,960, age 30-69, 100% M with diabetes	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.73 1.08 1.49	 0.52-1.00 0.86-1.36 1.15-1.93	Age, history of smoking, BMI, history of therapy for hypertension, dyslipidaemia or diabetes mellitus	High triglycerides (≥150 mg/dL)	- Among few studies investigating alcohol consumption among people with diabetes and MetS	- Men and middle ages only - Information of type of diabetes was not available - Information of diet, nutrition, physical activity, socioeconomic status were not available

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Wakabayashi et al. [141] Japan, 2011	N=7,250, age 35-65, 100% M with overweight and obesity	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.76 1.09 1.33	 0.65-0.90 0.97-1.22 1.17-1.52	Age, history of smoking, BMI, history of therapy for hypertension, dyslipidaemia or diabetes mellitus	High triglycerides (≥150 mg/dL)	- Among few studies investigating alcohol consumption among people with overweight and obesity and MetS	- Men & middle ages only - Information of type of alcohol beverages, diet, physical activity, socioeconomic status and race/ethnicity were not available
Hamaguchi et al. [114] Japan, 2012	N=18,571, age 18-88, mean 46.5 ± 9.9, 41% F	MetS - ATP III (men) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers MetS - ATP III (women) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers	 1.00 0.89 1.01 1.34 0.83 1.00 0.37 1.27 1.20 0.92	 0.76-1.03 0.87-1.18 1.16-1.56 0.49-1.40 0.19-0.74 0.68-2.35 0.45-3.20 0.43-1.99	Age, regular exercise, smoking, usage of drugs	High triglycerides (≥150 mg/dL) or on treatment	- Among few studies investigating alcohol consumption and MetS and fatty liver at the same time	- Self-reported information of alcohol intake may be underreporting - Generalizability to non-Japanese populations is uncertain - Not adjusting for dietary intakes

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Wakabayashi et al. [133] Japan, 2014	N=31,295, age 35-60, 100% M	Non-drinkers Occasional heavy drinkers Regular heavy drinkers	1.00 1.35 1.66	 1.12-1.64 1.41-1.96	Age, smoking, and regular exercise as other explanatory variables	High triglycerides (≥150 mg/dL)	- A unique finding of this study is that the positive association between alcohol and MetS was stronger in occasional heavy drinkers than in regular heavy drinkers, and thus, risk of MetS was suggested to be higher in the former group than in the latter group	- Men and middle ages only - Information on diet, nutrition, and socioeconomic factors were not available - Detailed information on the kind of alcohol beverage was also not available - Possibilities of differences in the relationships between heavy alcohol drinking and MetS by age, gender, and race/ethnicity - Unable to investigate cause-and-effect relationships
Hirakawa et al. [142] Japan, 2015	N=22,349, age 18-95, mean	Non-drinkers Light (<20 g/d) Heavy (≥20, <60 g/d) Very heavy (≥60 g/d)	1.00 0.96 1.16 1.37			High triglycerides (≥150 mg/dL)	- Attempt different definition of MetS (both international and adapted versions	- Men only - Non-drinkers included ex-drinkers

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
	48.6±10.2, 100% M						for Asian participants)	- Not adjusting for a range of potential confounders such as smoking, physical activity, dietary intakes - Not reporting relative ratios and 95% CIs
Cohort Studies								
Gigleux et al. [127] Canada, 2006	N=1,966 100% men, age 46-76	Alcohol consumption by quartile <1 g/d 1.3-5.4 g/d 5.5-15.1 g/d ≥15.2 g/d	 1.00 0.79 0.86 0.86	 0.61-1.01 0.68-1.12 0.67-1.12	Age, smoking habits, type 2 diabetes (presence or not), medication for hypertension (presence or absence)	High triglycerides (> 1.7 mmol/l)	- Prospective nature of the study	- Possible misclassification of alcohol intake due to self-report of intakes and change during follow-up - Drinking patterns were not evaluated - Not adjusting for physical activity as confounders
Baik et al. [134] Korea, 2008	N=3,833, age 40-69	Non-drinkers Very light (0.1-5 g/d) Light (5.1-15 g/d) Moderate (15.1-30 g/d) Heavy (>30 g/d)	1.00 0.88 0.97 1.31 1.60	 0.72-1.07 0.78-1.21 1.04-1.66 1.28-2.00	Age, sex, BMI, income, occupation, marital status, education, smoking status, quartiles	High triacylglycerol (≥150 mg/dL)	- Prospective nature of the study - A broad range of potential confounding factors	- Middle ages only - Limited data for beverage-specific drinkers

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
					of physical activity, energy intake, fat intake, dietary fiber intake, red meat intake, fish intake, nut intake, family history of diabetes, and family history of hypertension		were included in the analysis	
Buja et al. [135] Italy, 2010	N=1,321, Age 65-84, 100% M	At baseline (women)			Age, smoking, education and consumption of fish, coffee, vegetables, olive oil, cheese and cured meats	High triglycerides (≥150 mg/dL)	- Prospective nature part of the study - Draw from a large population-based sample	- Elderly only - Lack of information on the drinking patterns - Self-reporting of alcohol use - Small sample size of the incidence phase - Not adjusting for type of alcohol beverages
		Abstainers	1.00					
		<12 g/d	0.83	0.60-1.16				
		12-24 g/d	0.75	0.49-1.15				
		≥24 g/d	0.81	0.43-1.54				
		At baseline (men)						
		Abstainers	1.00					
		<12 g/d	1.28	0.74-2.19				
		12-24 g/d	1.08	0.64-1.82				
		25-47 g/d	1.08	0.62-1.87				
		≥48 g/d	1.25	0.69-2.26				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		At follow-up (women)						
		Abstainers	1.00					
		<12 g/d	0.90	0.43-1.73				
		12-24 g/d	0.44	0.14-1.30				
		≥24 g/d	0.34	0.03-2.23				
		At follow-up (men)						
		Abstainers	1.00					
		<12 g/d	2.07	0.39-6.40				
		12-24 g/d	1.34	0.21-5.00				
		25-47 g/d	2.18	0.42-6.70				
		≥48 g/d	1.13	0.16-5.19				
Kim et al. [136] Korea, 2012	N=4,505, age 23-81, 100% M	Alcohol consumption status at baseline			Age, baseline weight, lifestyle (diet, smoking, and exercise), and each component of MetS at baseline, LDL-C, hsCRP, ALT, uric acid, and HOMA-IR values	High triglycerides (≥150 mg/dL)	- Prospective nature - Analysed the effects of changes in alcohol consumption during a follow-up period, as well as the status of baseline alcohol consumption, on the	- Men only - Not fully representative of general population because most subjects were urban residents - Possibility of underreporting of alcohol use due to self-reported information
		Non-drinkers	1.00					
		Light (1.0-14.9 g/d)	1.27	0.94-1.71				
		Moderate (15.0-29.9 g/d)	2.03	1.42-2.90				
		Heavy (≥30 g/d)	1.74	1.05-2.88				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							incidence of MetS and each component of MetS	- Unable to analyse the effects of beverage type - Lack information of smoking and dietary factors - Changed alcohol consumption status might be misclassified because alcohol consumption status and MetS were assessed only at baseline and at the end of the 3-year follow-up
Shuval et al. [77] USA, 2012	N=3,411, age mean 42.3 ± 8.6, 100% M	Non-drinkers Light (≤3 drinks/w) Moderate (>3-14 drinks/w) Heavy (>14 drinks/w)	1.00 1.00 1.01 1.04	 0.69-1.46 0.72-1.43 0.77-1.39	Age, examination year, smoking status, family history of CVD, BMI, and cardiorespiratory fitness	Elevated triglycerides (≥150 mg/dL)	- Prospective nature - Among few studies investigating joint effect of alcohol consumption & cardiorespiratory fitness and MetS	- Men only - Limit ability to generalise findings due to selection bias of mostly white & well-educated participants - Quantity of alcohol intake, drinking patterns (e.g. binge drinking) were not assessed - Non-drinkers included both current and lifetime

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								abstainers who may have differ cardio-metabolic risks - Lack of dietary information
Stoutenberg et al. [128] USA, 2013	N=7,483, age 20-100, mean 43.4 ± 9.0, 100% men	Non-drinkers Light (1-3 drinks/w) Moderate (4-7 drinks/w) Moderate-heavy (8-13 drinks/w) Heavy (14+ drinks/w)	1.00 0.87 0.88 0.88 0.96	 0.72-1.05 0.75-1.07 0.73-1.06 0.81-1.15	Age, year of examination, smoking, maximal treadmill time (min)	High triglycerides (≥15 mg/l)	- Comprehensive physical examination and an extensive follow-up period in one of the largest cohort studies - Ability to stratify and adjust our models using cardiorespiratory fitness rather than self-reported physical activity - One of the first prospective studies examining the relationship between	- Participants are males only - Limited external validity beyond Caucasian males of a higher socio-economic status - Possibility of under-reporting and subsequent misclassification of alcohol consumption - Potential misclassification of the reference group as former drinkers and lifetime abstainers have very different alcohol consumption histories - In the stratified analyses, the relatively small

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							AC and MetS in a US male population	number of incident MetS cases in the older, normal-weight (BMI, 25 kg/m2), healthy and least fit groups may have affected the results in these groups

Table 1-12. Alcohol consumption and the risk of high blood pressure, summary of studies

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Cross-sectional Studies								
Djousse et al. [124] USA, 2004	N=4,510, Age (mean 51.6 ± 13.7, range: 25-91), all white, 54% F	Never drinkers Former drinkers (men) Current drinkers (men) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d Former drinkers (women) Current drinkers (women) 0.1-2.5 g/d 2.6-12.0 g/d 12.1-24.0 g/d >24.0 g/d	1.00 1.15 0.81 0.80 1.17 1.85 0.88 0.77 0.74 1.21 1.41	 0.83-1.60 0.45-1.46 0.53-1.21 0.75-1.81 1.21-2.84 0.67-1.15 0.42-1.39 0.52-1.08 0.78-1.86 0.80-2.48	Age, age squared, sex, center, risk group (random versus high risk for CHD), current smoking, education, physical activity, and fruit and vegetable intake	Hypertension	- Adjustments for a range of potential confounders	- Unable to investigate cause-and-effect relationships - Not adjusting for types of alcoholic beverages
Freiberg et al. [125] USA, 2004	N=8,125, Age >20, mean 42.7 ± 0.5 (men), 45.2 ± 0.6	< 1 (drinks/month) 1-19 (drinks/month) ≥20 (drinks/month)	1.00 0.69 0.22	 0.60-0.78 0.16-0.29	Age, sex, race/ethnicity, income, tobacco use, physical activity, diet	Hypertension (blood pressure ≥ 130/85 mmHg or antihypertensive medication)	- Large sample size - Assessment of effect modification by race/ethnicity	- Not adjusting for types of alcoholic beverages - Possibility of misdiagnosis of diabetes due to different definitions of patients with hypertension

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
	(women), 52% F							
Yoon et al. [137] Korea, 2004	N=7,962 Age mean 44.2 ± 14.8 (men), 45.1 ± 16.0 (women), 55% F	Non-drinkers Drinkers (men) 1-14.9 g/d 15-29.9 g/d 30-79.9 g/d ≥80 g/d Drinkers (women) 1-14.9 g/d 15-29.9 g/d ≥30 g/d	1.00 0.96 1.29 1.45 1.88 0.88 1.71 1.77	 0.76-1.21 0.98-1.69 1.12-1.87 1.32-2.68 0.73-1.06 1.10-2.64 0.93-3.38	Sex, age, marital status, education level, smoking status, exercise, household income, waist circumference, BMI, energy intake	High blood pressure		- Ex-drinkers included in the non-drinkers group. - No adjustments for specific types of alcoholic beverages - Recall bias due to self-reported interview
Fan et al. [129] USA, 2005	N=2,818, Age 35-80, mean 55.4 ± 11.1, 59% F, 93% white	Drinking intensity in quartiles (drinks/drinking day) Q1 Q2 Q3 Q4 Drinking frequency in quartiles (in days)	 1.00 1.16 1.45 1.63	 0.88-1.53 1.10-1.90 1.15-2.31	Age, race, family history of coronary heart disease and diabetes, years of education, lifetime cigarette pack-years, current smoking and drinking status,	High blood pressure (NCEP ATP III)	- Among few studies investigating lifetime drinking patterns and differentiating cardiovascular risk - Measure drinking intensity (drinks or grams/day) along with average	- Middle ages & elderly only - Only recent measures for dietary factors (12-24 months prior to interview) - Other residual confounding was possibly failed to be included - Uncertain reports by elderly people (>80)

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		Q1 Q2 Q3 Q4	1.00 1.14 1.17 1.17	 0.86-1.50 0.88-1.57 0.86-1.59	quartiles of lifetime and current physical activity, total energy intake, percentage of energy intake from saturated fat, and dietary fiber intake		consumption (like most of studies) - Adjusting for a range of potential confounders	- Other drinking patterns such as drinking with meals and beverage preference were not included in the analysis
Fan et al. [126] China, 2008	N=3,953, age 20-88, 68% F	Non-drinkers Light (1-9.9 g/d) Moderate (10-29.9 g/d) Excessive (≥30 g/d)	1.00 1.28 1.17 1.34		Demographics, BMI	High BP: the 7th report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of HBP (JNC7)	- Large sample size	- None reporting of relative ratios and 95% CI - Not adjusting for a range of potential confounders such as smoking, physical activity, type of beverages in multivariable regression analysis
Takeuchi et al. [112] Japan, 2009	N=1,215, age 20-67, mean 42.5 ± 10.3, 100% M	Drinking Smoking and drinking	1.2 0.9	0.8-1.6 0.7-1.1	Age, previous coronary artery disease, exercise, insomnia, and stress perception	High BP: systolic and diastolic BP ≥ 130 and ≥ 85 mmHg	- Measure interaction between smoking and alcohol intake	- Men only - Self-rated alcohol consumption may lead to underreporting

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								- Number of subjects was relatively small - Not adjusting for smoking, dietary intake
Kahl et al. [131] Germany, 2010	N=197, age ≥18, 33% F	Alcohol dependence Alcohol dependence (men) Alcohol dependence (women)	1.30 1.19 1.46		Age and sex-standardized according to the German population 2004	High BP: ≥130/85 mmHg	- Among few studies investigating alcohol dependence and MetS	- Carry-over effects of alcohol withdrawal - Not reporting relative ratios (ORs) and 95% CI - Insufficient or no information about eating habits and educational level
Nakashita et al. [116] Japan, 2010	N=3,904, age ≥ 20, 100% M	Non-drinkers 0.1-22.9 g/d 23-45.9 g/d 46-69 g/d ≥69 g/d	1.00 1.14 1.79 2.09 3.09	 0.93-1.41 1.43-2.23 1.61-2.72 2.27-4.19	Age, eating habits, regular exercise, and smoking	High BP ≥130/85 mmHg or use of antihypertensive medication		- Men only - Possibility of misdiagnosis of high BP due to different criteria
Wakabayashi et al. [113] Japan, 2010	N=30,585, age 30-54, 37% F	Non-drinkers (men) Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d) Non-drinkers (women)	1.00 1.43 1.77 2.42 1.00	 1.29-1.59 1.64-1.91 2.22-2.65	Age, history of smoking, BMI, history of therapy for hypertension,	High BP: systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg		- Middle ages only - Not adjusting for nutrition, food intake, physical activity, drinking pattern, and the type of alcohol beverage

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
		Light (<22 g/d) Heavy (≥22 g/d)	1.09 1.74	0.89-1.35 1.48-2.06	dyslipidaemia or diabetes mellitus			- Possibility of misdiagnosis of high BP due to different criteria
Kim et al. [132] Korea, 2011	N=714, age 40-59, 100% M	Alcohol use behaviours (using AUDIT by WHO) Normal Hazardous Problem	 1.00 2.54 2.99	 1.59-4.06 1.83-4.92	Education, smoking, physical activity	High BP: systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg	- Among few studies investigating alcohol use behaviours using AUDIT - From a large pool of population-based data	- Men & middle ages only - Impossible to examine the effects of light alcohol use on MetS components - Missing data limited the generalizability of the study findings - Selection bias due to the exclusion of subjects with missing value
Wakabayashi et al. [140] Japan, 2011	N=1,960, age 30-69, 100% M with diabetes	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 1.49 2.52 2.88	 1.02-2.19 1.90-3.35 2.05-4.05	Age, history of smoking, BMI, history of therapy for hypertension, dyslipidaemia or diabetes mellitus	High BP: systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg	- Among few studies investigating alcohol consumption among people with diabetes and MetS	- Men and middle ages only - Information of type of diabetes was not available - Information of diet, nutrition, physical activity, socioeconomic status were not available

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Wakabayashi et al. [141] Japan, 2011	N=7,250, age 35-65, 100% M with overweight and obesity	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 1.73 2.00 2.57	 1.43-2.11 1.74-2.29 2.18-3.03	Age, history of smoking, BMI, history of therapy for hypertension, dyslipidaemia or diabetes mellitus	High BP: systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg	- Among few studies investigating alcohol consumption among people with overweight and obesity and MetS	- Men & middle ages only - Information of type of alcohol beverages, diet, physical activity, socioeconomic status and race/ethnicity were not available
Hamaguchi et al. [114] Japan, 2012	N=18,571, age 18-88, mean 46.5 ± 9.9, 41% F	MetS - ATP III (men) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers MetS - ATP III (women) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers	 1.00 1.33 1.47 2.24 1.09 1.00 1.22 1.97 3.13 0.72	 1.16-1.53 1.27-1.70 1.93-2.59 0.68-1.73 0.85-1.75 1.26-3.07 1.71-5.72 0.42-1.23	Age, regular exercise, smoking, usage of drugs	High BP: systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg	- Among few studies investigating alcohol consumption and MetS and fatty liver at the same time	- Self-reported information of alcohol intake may be underreporting - Generalizability to non-Japanese populations is uncertain - Not adjusting for dietary intakes

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Wakabayashi et al. [133] Japan, 2014	N=31,295, age 35-60, 100% M	Non-drinkers Occasional heavy drinkers Regular heavy drinkers	1.00 1.63 2.83	 1.32-2.00 2.37-3.38	Age, smoking, and regular exercise as other explanatory variables	High BP: systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg	- A unique finding of this study is that the positive association between alcohol and MetS was stronger in occasional heavy drinkers than in regular heavy drinkers, and thus, risk of MetS was suggested to be higher in the former group than in the latter group	- Men and middle ages only - Information on diet, nutrition, and socioeconomic factors were not available - Detailed information on the kind of alcohol beverage was also not available - Possibilities of differences in the relationships between heavy alcohol drinking and MetS by age, gender, and race/ethnicity - Unable to investigate cause-and-effect relationships
Hirakawa et al. [142]	N=22,349, age 18-95, mean	Systolic BP ≥ 130 mmHg Non-drinkers Light (<20 g/d) Heavy (≥20, <60 g/d)	 1.00 0.98 1.44			High BP (systolic BP ≥ 130 mmHg/ diastolic BP ≥ 85 mmHg)	- Attempt different definition of MetS (both international and adapted versions	- Men only - Non-drinkers included ex-drinkers

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Japan, 2015	48.6±10.2, 100% M	Very heavy (≥60 g/d) Diastolic BP ≥ 85 mmHg	1.59				for Asian participants)	- Not adjusting for a range of potential confounders such as smoking, physical activity, dietary intakes - Not reporting relative ratios and 95% CIs
		Non-drinkers	1.00					
		Light (<20 g/d)	1.10					
		Heavy (≥20, <60 g/d)	1.38					
		Very heavy (≥60 g/d)	1.68					
Cohort Studies								
Gigleux et al. [127] Canada, 2006	N=1,966 100% men, age 46-76	Alcohol consumption by quartile			Age, smoking habits, type 2 diabetes (presence or not), medication for hypertension (presence or absence)	Systolic blood pressure (> 133 mmHg)	- Prospective nature of the study	- Possible misclassification of alcohol intake due to self-report of intakes and change during follow-up - Drinking patterns were not evaluated - Not adjusting for physical activity as confounders
		<1 g/d	1.00					
		1.3-5.4 g/d	0.96	0.74-1.25				
		5.5-15.1 g/d	0.96	0.74-1.25				
		≥15.2 g/d	1.40	1.05-1.78				
Baik et al. [134] Korea, 2008	N=3,833, age 40-69	Non-drinkers	1.00		Age, sex, BMI, income, occupation, marital status, education, smoking status, quartiles	High blood pressure (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg)	- Prospective nature of the study - A broad range of potential confounding factors	- Middle ages only - Limited data for beverage-specific drinkers
		Very light (0.1-5 g/d)	0.96	0.76-1.20				
		Light (5.1-15 g/d)	1.23	0.96-1.59				
		Moderate (15.1-30 g/d)	2.21	1.71-2.86				
		Heavy (>30 g/d)	2.19	1.70-2.82				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
					of physical activity, energy intake, fat intake, dietary fiber intake, red meat intake, fish intake, nut intake, family history of diabetes, and family history of hypertension		were included in the analysis	
Buja et al. [135] Italy, 2010	N=1,321, Age 65-84, 100% M	At baseline (women)			Age, smoking, education and consumption of fish, coffee, vegetables, olive oil, cheese and cured meats	Systolic pressure ≥130 mmHg or diastolic pressure ≥85 mmHg	- Prospective nature part of the study - Draw from a large population-based sample	- Elderly only - Lack of information on the drinking patterns - Self-reporting of alcohol use - Small sample size of the incidence phase - Not adjusting for type of alcohol beverages
		Abstainers	1.00					
		<12 g/d	0.88	0.50-1.56				
		12-24 g/d	1.08	0.52-2.25				
		≥24 g/d	1.96	0.55-6.99				
		At baseline (men)						
		Abstainers	1.00					
		<12 g/d	2.33	1.09-4.97				
		12-24 g/d	1.31	0.66-2.60				
		25-47 g/d	1.19	0.59-2.42				
		≥48 g/d	5.42					

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		At follow-up (women)		1.84-				
		Abstainers	1.00	15.93				
		<12 g/d	1.20					
		12-24 g/d	0.82					
		≥24 g/d	-	0.31-1.36				
		At follow-up (men)		0.10-1.33				
		Abstainers	1.00	-				
		<12 g/d	1.43					
		12-24 g/d	1.29					
		25-47 g/d	1.62	0.61-1.72				
		≥48 g/d	0.93	0.47-1.69				
				0.90-1.76				
				0.10-1.69				
Kim et al. [136] Korea, 2012	N=4,505, age 23-81, 100% M	Alcohol consumption status at baseline			Age, baseline weight, lifestyle (diet, smoking, and exercise), and each component of MetS at baseline, LDL-C, hsCRP, ALT, uric	High BP (systolic/diastolic BP ≥130/85 mmHg)	- Prospective nature - Analysed the effects of changes in alcohol consumption during a follow-up period, as well as the status of	- Men only - Not fully representative of general population because most subjects were urban residents - Possibility of underreporting of alcohol use
		Non-drinkers	1.00					
		Light (1.0-14.9 g/d)	0.71	0.53-0.96				
		Moderate (15.0-29.9 g/d)	0.42	0.28-0.64				
		Heavy (≥30 g/d)	0.33	0.16-0.66				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
					acid, and HOMA-IR values		baseline alcohol consumption, on the incidence of MetS and each component of MetS	due to self-reported information - Unable to analyse the effects of beverage type - Lack information of smoking and dietary factors - Changed alcohol consumption status might be misclassified because alcohol consumption status and MetS were assessed only at baseline and at the end of the 3-year follow-up
Shuval et al. [77] USA, 2012	N=3,411, age mean 42.3 ± 8.6, 100% M	Non-drinkers Light (≤3 drinks/w) Moderate (>3-14 drinks/w) Heavy (>14 drinks/w)	1.00 0.71 0.87 0.86	 0.56-0.91 0.70-1.08 0.71-1.04	Age, examination year, smoking status, family history of CVD, BMI, and cardiorespiratory fitness	Elevated Blood Pressure (≥130/85 mmHg)	- Prospective nature - Among few studies investigating joint effect of alcohol consumption & cardiorespiratory fitness and MetS	- Men only - Limit ability to generalise findings due to selection bias of mostly white & well-educated participants - Quantity of alcohol intake, drinking patterns (e.g. binge drinking) were not assessed

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								- Non-drinkers included both current and lifetime abstainers who may have differ cardio-metabolic risks - Lack of dietary information
Stoutenberg et al. [128] USA, 2013	N=7,483, age 20-100, mean 43.4 ± 9.0, 100% men	Non-drinkers Light (1-3 drinks/w) Moderate (4-7 drinks/w) Moderate-heavy (8-13 drinks/w) Heavy (14+ drinks/w)	1.00 0.94 0.93 0.97 1.09	 0.80-1.10 0.80-1.09 0.83-1.14 0.94-1.28	Age, year of examination, smoking, maximal treadmill time (min)	High BP (≥130/85 mmHg)	- Comprehensive physical examination and an extensive follow-up period in one of the largest cohort studies - Ability to stratify and adjust our models using cardiorespiratory fitness rather than self-reported physical activity - One of the first prospective studies examining the	- Participants are males only - Limited external validity beyond Caucasian males of a higher socio-economic status - Possibility of under-reporting and subsequent misclassification of alcohol consumption - Potential misclassification of the reference group as former drinkers and lifetime abstainers have very different alcohol consumption histories

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							relationship between AC and MetS in a US male population	- In the stratified analyses, the relatively small number of incident MetS cases in the older, normal-weight (BMI, 25 kg/m2), healthy and least fit groups may have affected the results in these groups

Table 1-13. Alcohol consumption and the risk of high levels of blood/plasma glucose, summary of studies

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Cross-sectional Studies								
Freiberg et al. [125] USA, 2004	N=8,125, Age >20, mean 42.7 ± 0.5 (men), 45.2 ± 0.6 (women), 52% F	< 1 (drinks/month) 1-19 (drinks/month) ≥20 (drinks/month)	1.00 0.69 0.22	 0.60-0.78 0.16-0.29	Age, sex, race/ethnicity, income, tobacco use, physical activity, diet	Fasting blood glucose ≥ 6.1 mmol/l or antidiabetic medication	- Large sample size - Assessment of effect modification by race/ethnicity	- Unable to investigate cause-and-effect relationships - Not adjusting for types of alcoholic beverages - Possibility of misdiagnosis of diabetes due to different definitions of patients with high levels of glucose
Yoon et al. [137] Korea, 2004	N=7,962 Age mean 44.2 ± 14.8 (men), 45.1 ± 16.0 (women), 55% F	Non-drinkers Drinkers (men) 1-14.9 g/d 15-29.9 g/d 30-79.9 g/d ≥80 g/d Drinkers (women) 1-14.9 g/d 15-29.9 g/d ≥30 g/d	1.00 0.86 1.19 0.92 0.94 0.86 0.84 2.12	 0.76-1.21 0.66-1.12 0.69-1.23 0.64-1.39 0.70-1.05 0.51-1.37 1.13-3.97	Sex, age, marital status, education level, smoking status, exercise, household income, waist circumference, BMI, energy intake	High fasting blood glucose		- Ex-drinkers included in the non-drinkers group. - No adjustments for specific types of alcoholic beverages - Recall bias due to self-reported interview

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Fan et al. [129] USA, 2005	N=2,818, Age 35-80, mean 55.4 ± 11.1, 59% F, 93% white	Drinking intensity in quartiles (drinks/drinking day) Q1 Q2 Q3 Q4 Drinking frequency in quartiles (in days) Q1 Q2 Q3 Q4	 1.00 1.18 1.37 1.42 1.00 0.92 0.78 0.95	 0.90-1.54 1.05-1.79 1.02-1.98 0.71-1.19 0.59-1.03 0.71-1.27	Age, race, family history of coronary heart disease and diabetes, years of education, lifetime cigarette pack-years, current smoking and drinking status, quartiles of lifetime and current physical activity, total energy intake, percentage of energy intake from saturated fat, and dietary fiber intake	Impaired fasting glucose IFG (NCEP ATP III)	- Among few studies investigating lifetime drinking patterns and differentiating cardiovascular risk - Measure drinking intensity (drinks or grams/day) along with average consumption (like most of studies) - Adjusting for a range of potential confounders	- Middle ages & elderly only - Only recent measures for dietary factors (12-24 months prior to interview) - Other residual confounding was possibly failed to be included - Uncertain reports by elderly people (>80) - Other drinking patterns such as drinking with meals and beverage preference were not included in the analysis
Fan et al. [126] China, 2008	N=3,953, age 20-88, 68% F	Non-drinkers Light (1-9.9 g/d) Moderate (10-29.9 g/d) Excessive (≥30 g/d)	1.00 0.88 1.11 0.94		Demographics, BMI	IFG: WHO/NCD/NCS/ 99.2 (1999)	- Large sample size	- Non-reporting of relative ratios and 95% CI - Not adjusting for a range of potential confounders such as smoking, physical activity, type of beverages in

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								multivariable regression analysis
Takeuchi et al. [112] Japan, 2009	N=1,215, age 20-67, mean 42.5 ± 10.3, 100% M	Drinking Smoking and drinking	1.7 1.1	1.1-2.6 0.8-1.5	Age, previous coronary artery disease, exercise, insomnia, and stress perception	High fasting blood glucose: ≥100 mg/dL	- Measure interaction between smoking and alcohol intake	- Men only - Self-rated alcohol consumption may lead to underreporting - Number of subjects was relatively small - Not adjusting for smoking, dietary intake
Kahl et al. [131] Germany, 2010	N=197, age ≥18, 33% F	Alcohol dependence Alcohol dependence (men) Alcohol dependence (women)	3.35 2.54 4.99		Age and sex-standardized according to the German population 2004	High fasting blood glucose: ≥100 mg/dL	- Among few studies investigating alcohol dependence and MetS	- Carry-over effects of alcohol withdrawal - Not reporting relative ratios (ORs) and 95% CI - Insufficient or no information about eating habits and educational level
Nakashita et al. [116]	N=3,904, age ≥ 20, 100% M	Non-drinkers 0.1-22.9 g/d 23-45.9 g/d 46-69 g/d	1.00 0.94 1.15 1.02	 0.61-1.57 0.68-1.92 0.55-1.91	Age, eating habits, regular exercise, and smoking	High fasting plasma glucose ≥100 mg/dL or		- Men only - Possibility of misdiagnosis of impaired glucose due to different criteria

Author	**Sample**	**Alcohol consumption status**	**OR**	**95% CI**	**Adjustments**	**Measurements of outcome(s)**	**Strengths**	**Limitations**
Japan, 2010		≥69 g/d	1.51	0.77-2.96		use of antidiabetic medication		
Wakabayashi et al. [113] Japan, 2010	N=30,585, age 30-54, 37% F	Non-drinkers (men) Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d) Non-drinkers (women) Light (<22 g/d) Heavy (≥22 g/d)	1.00 0.62 0.66 0.73 1.00 0.30 0.58	 0.46-0.82 0.55-0.80 0.59-0.90 0.09-1.01 0.28-1.21	Age, history of smoking, BMI, history of therapy for hypertension, dyslipidaemia or diabetes mellitus	High haemoglobin A1c		- Middle ages only - Not adjusting for nutrition, food intake, physical activity, drinking pattern, and the type of alcohol beverage
Kim et al. [132] Korea, 2011	N=714, age 40-59, 100% M	Alcohol use behaviours (using AUDIT by WHO) Normal Hazardous Problem	 1.00 2.15 2.48	 1.16-3.99 1.42-4.33	Education, smoking, physical activity	High fasting plasma glucose ≥110 mg/dL	- Among few studies investigating alcohol use behaviours using AUDIT - From a large pool of population-based data	- Men & middle ages only - Impossible to examine the effects of light alcohol use on MetS components - Missing data limited the generalizability of the study findings - Selection bias due to the exclusion of subjects with missing value

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Wakabayashi et al. [141] Japan, 2011	N=7,250, age 35-65, 100% M with overweight and obesity	Non-drinkers Light (<22 g/d) Heavy (≥22, <44 g/d) Very heavy (≥44 g/d)	1.00 0.82 0.62 0.71	 0.64-1.03 0.52-0.73 0.59-0.86	Age, history of smoking, BMI, history of therapy for hypertension, dyslipidaemia or diabetes mellitus	High haemoglobin A1c	- Among few studies investigating alcohol consumption among people with overweight and obesity and MetS	- Men & middle ages only - Information of type of alcohol beverages, diet, physical activity, socioeconomic status and race/ethnicity were not available
Hamaguchi et al. [114] Japan, 2012	N=18,571, age 18-88, mean 46.5 ± 9.9, 41% F	MetS - ATP III (men) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers MetS - ATP III (women) Non-drinkers Light (40-140 g/w) Moderate (140-280 g/w) Excess (>280 g/w) Wine consumers	 1.00 1.00 1.23 1.38 1.78 1.00 1.52 1.46 2.66 0.56	 0.88-1.13 1.08-1.40 1.20-1.58 1.17-2.72 1.11-2.08 0.95-2.25 1.49-4.76 0.33-0.96	Age, regular exercise, smoking, usage of drugs	High fasting plasma glucose ≥100 mg/dL	- Among few studies investigating alcohol consumption and MetS and fatty liver at the same time	- Self-reported information of alcohol intake may be underreporting - Generalizability to non-Japanese populations is uncertain - Not adjusting for dietary intakes

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Wakabayashi et al. [133] Japan, 2014	N=31,295, age 35-60, 100% M	Non-drinkers Occasional heavy drinkers Regular heavy drinkers	1.00 0.86 0.66	 0.60-1.24 0.46-0.95	Age, smoking, and regular exercise as other explanatory variables	Hyperglycaemia	- A unique finding of this study is that the positive association between alcohol and MetS was stronger in occasional heavy drinkers than in regular heavy drinkers, and thus, risk of MetS was suggested to be higher in the former group than in the latter group	- Men and middle ages only - Information on diet, nutrition, and socioeconomic factors were not available - Detailed information on the kind of alcohol beverage was also not available - Possibilities of differences in the relationships between heavy alcohol drinking and MetS by age, gender, and race/ethnicity - Unable to investigate cause-and-effect relationships
Hirakawa et al. [142]	N=22,349, age 18-95, mean	Waist – ATP III (>102 cm) Non-drinkers Light (<20 g/d)	 1.00 0.60 0.65			Waist >102 cm (NCEP ATP III)	- Attempt different definition of MetS (both international and adapted versions	- Men only - Non-drinkers included ex-drinkers

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
Japan, 2015	48.6±10.2, 100% M	Heavy (≥20, <60 g/d) Very heavy (≥60 g/d) Waist – IDF (≥90 cm) Non-drinkers Light (<20 g/d) Heavy (≥20, <60 g/d) Very heavy (≥60 g/d) Waist – Japanese (≥85 cm) Non-drinkers Light (<20 g/d) Heavy (≥20, <60 g/d) Very heavy (≥60 g/d)	1.20 1.00 0.84 1.08 1.32 1.00 0.87 1.02 1.12			Waist ≥90 cm or BMI >30 kg/m^2 (IDF) Waist ≥85 cm (Japanese criteria of MetS)	for Asian participants)	- Not adjusting for a range of potential confounders such as smoking, physical activity, dietary intakes - Not reporting relative ratios and 95% CIs
Cohort Studies								
Baik et al. [134] Korea, 2008	N=3,833, age 40-69	Non-drinkers Very light (0.1-5 g/d) Light (5.1-15 g/d) Moderate (15.1-30 g/d) Heavy (>30 g/d)	1.00 0.81 0.85 1.57 2.37	 0.50-1.32 0.49-1.45 0.96-2.58 1.50-3.73	Age, sex, BMI, income, occupation, marital status, education, smoking status, quartiles of physical activity, energy intake, fat	High glucose (fasting glucose ≥110 mg/dL)	- Prospective nature of the study - A broad range of potential confounding factors were included in the analysis	- Middle ages only - Limited data for beverage-specific drinkers

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
					intake, dietary fiber intake, red meat intake, fish intake, nut intake, family history of diabetes, and family history of hypertension			
Buja et al. [135] Italy, 2010	N=1,321, Age 65-84, 100% M	At baseline (women) Abstainers <12 g/d 12-24 g/d ≥24 g/d At baseline (men) Abstainers <12 g/d 12-24 g/d 25-47 g/d ≥48 g/d At follow-up (women) Abstainers	 1.00 0.77 1.16 1.30 1.00 1.06 1.09 0.87 1.42 1.00	 0.51-1.17 0.71-1.89 0.67-1.80 0.56-2.00 0.59-2.02 0.46-1.66 0.73-2.78 	Age, smoking, education and consumption of fish, coffee, vegetables, olive oil, cheese and cured meats	High glucose (fasting glucose ≥110 mg/dL)	- Prospective nature part of the study - Draw from a large population-based sample	- Elderly only - Lack of information on the drinking patterns - Self-reporting of alcohol use - Small sample size of the incidence phase - Not adjusting for type of alcohol beverages

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
		<12 g/d	1.15	0.59-2.18				
		12-24 g/d	1.45	0.63-3.01				
		≥24 g/d	0.41	0.05-2.79				
		At follow-up (men)						
		Abstainers	1.00					
		<12 g/d	5.04	0.66-				
		12-24 g/d	4.92	25.11				
		25-47 g/d	6.71	0.66-				
		≥48 g/d	4.49	24.31				
				0.93-				
				29.27				
				0.56-				
				23.78				
Kim et al. [136] Korea, 2012	N=4,505, age 23-81, 100% M	Alcohol consumption status at baseline			Age, baseline weight, lifestyle (diet, smoking, and exercise), and each component of MetS at baseline, LDL-C, hsCRP, ALT, uric	High glucose (fasting glucose ≥110 mg/dL)	- Prospective nature - Analysed the effects of changes in alcohol consumption during a follow-up period, as well as the status of	- Men only - Not fully representative of general population because most subjects were urban residents - Possibility of underreporting of alcohol use
		Non-drinkers	1.00					
		Light (1.0-14.9 g/d)	1.18	0.82-1.69				
		Moderate (15.0-29.9 g/d)	1.60	1.05-2.44				
		Heavy (≥30 g/d)	1.59	0.88-2.87				

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
					acid, and HOMA-IR values		baseline alcohol consumption, on the incidence of MetS and each component of MetS	due to self-reported information - Unable to analyse the effects of beverage type - Lack information of smoking and dietary factors - Changed alcohol consumption status might be misclassified because alcohol consumption status and MetS were assessed only at baseline and at the end of the 3-year follow-up
Shuval et al. [77] USA, 2012	N=3,411, age mean 42.3 ± 8.6, 100% M	Non-drinkers Light (≤3 drinks/w) Moderate (>3-14 drinks/w) Heavy (>14 drinks/w)	1.00 0.81 0.82 0.99	 0.63-1.04 0.65-1.04 0.82-1.20	Age, examination year, smoking status, family history of CVD, BMI, and cardiorespiratory fitness	Elevated fasting glucose (≥100 mmHg)	- Prospective nature - Among few studies investigating joint effect of alcohol consumption & cardiorespiratory fitness and MetS	- Men only - Limit ability to generalise findings due to selection bias of mostly white & well-educated participants - Quantity of alcohol intake, drinking patterns (e.g. binge drinking) were not assessed

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
								- Non-drinkers included both current and lifetime abstainers who may have differ cardio-metabolic risks - Lack of dietary information
Stoutenberg et al. [128] USA, 2013	N=7,483, age 20-100, mean 43.4 ± 9.0, 100% men	Non-drinkers Light (1-3 drinks/w) Moderate (4-7 drinks/w) Moderate-heavy (8-13 drinks/w) Heavy (14+ drinks/w)	1.00 1.06 1.28 1.22 1.56	 0.91-1.24 1.11-1.48 0.83-1.14 1.35-1.81	Age, year of examination, smoking, maximal treadmill time (min)	High glucose (fasting glucose ≥11 mg/l)	- Comprehensive physical examination and an extensive follow-up period in one of the largest cohort studies - Ability to stratify and adjust our models using cardiorespiratory fitness rather than self-reported physical activity - One of the first prospective studies examining the	- Participants are males only - Limited external validity beyond Caucasian males of a higher socio-economic status - Possibility of under-reporting and subsequent misclassification of alcohol consumption - Potential misclassification of the reference group as former drinkers and lifetime abstainers have very different alcohol consumption histories

Author	Sample	Alcohol consumption status	OR	95% CI	Adjustments	Measurements of outcome(s)	Strengths	Limitations
							relationship between AC and MetS in a US male population	- In the stratified analyses, the relatively small number of incident MetS cases in the older, normal-weight (BMI , 25 kg/m2), healthy and least fit groups may have affected the results in these groups
Hirakawa et al. [142] Japan, 2015	N=22,349, age 18-95, mean 48.6±10.2, 100% M	FPG ≥100 mg/dL				Fasting plasma glucose (FPG) ≥100 mg/dL (NCEP ATP III & IDF) FPG ≥110 mg/dL (Japanese criteria)	- Attempt different definition of MetS (both international and adapted versions for Asian participants)	- Men only - Non-drinkers included ex-drinkers - Not adjusting for a range of potential confounders such as smoking, physical activity, dietary intakes - Not reporting relative ratios and 95% CIs
		Non-drinkers	1.00					
		Light (<20 g/d)	0.96					
		Heavy (≥20, <60 g/d)	1.19					
		Very heavy (≥60 g/d)	1.21					
		FPG ≥110 mg/dL						
		Non-drinkers	1.00					
		Light (<20 g/d)	0.93					
		Heavy (≥20, <60 g/d)	1.15					
		Very heavy (≥60 g/d)	1.32					

Chapter 2

Methods

2 Chapter 2. Methods

2.1. Introduction

This chapter provides information on the methods for the Childhood Determinants of Adult Health (CDAH) study and the 1985 Australian Schools Health and Fitness Survey (ASHFS) that formed the baseline assessment for CDAH. Data from these studies are used for the analyses presented within this thesis. Detailed information on the measurements used as exposures, outcomes and covariates are provided in the different results chapters. The information provided in this chapter provides an overview of the study and its methods.

The CDAH study is prospective, longitudinal cohort study that began with the 1985 Australian Schools Health and Fitness Survey (ASHFS). The 1985 ASHFS collected an extensive range of lifestyle, physical and biological measures on a nationally representative sample of 8,498 Australian schoolchildren aged 7-15 years. The aims of the CDAH study are to determine the contribution of childhood risk factors to the development of cardio-metabolic diseases in adulthood.

The 1985 ASHFS was approved by the State Directors General of Education. The CDAH follow-up study was approved by the Southern Tasmania Health and Medical Research Ethics Committee.

2.2. The 1985 Australian School Health and Fitness Survey (ASHFS)

2.2.1. Sampling and participants

The 1985 ASHFS was conducted on a nationally representative sample of 8,498 Australian schoolchildren aged 7-15 years. The sampling procedure was reported elsewhere [167]. Briefly, these children were selected using two-stage random sampling. Stage 1 was the selection of schools with a probability proportional to enrolment numbers. Schools with total enrolment of less than 200 students (9.9% of primary schools and 3.1% of secondary schools) were excluded. Of the 121 schools selected, 90.1% (109/121) agreed to participate. The distribution of participating schools is shown in Figure 2-1. Stage 2 was the selection of children within each school with age and sex stratification. The study aimed for 500 boys and

500 girls from each year of age. Of the 12,578 schoolchildren invited, 8,498 (67.5%) children participated in the study.

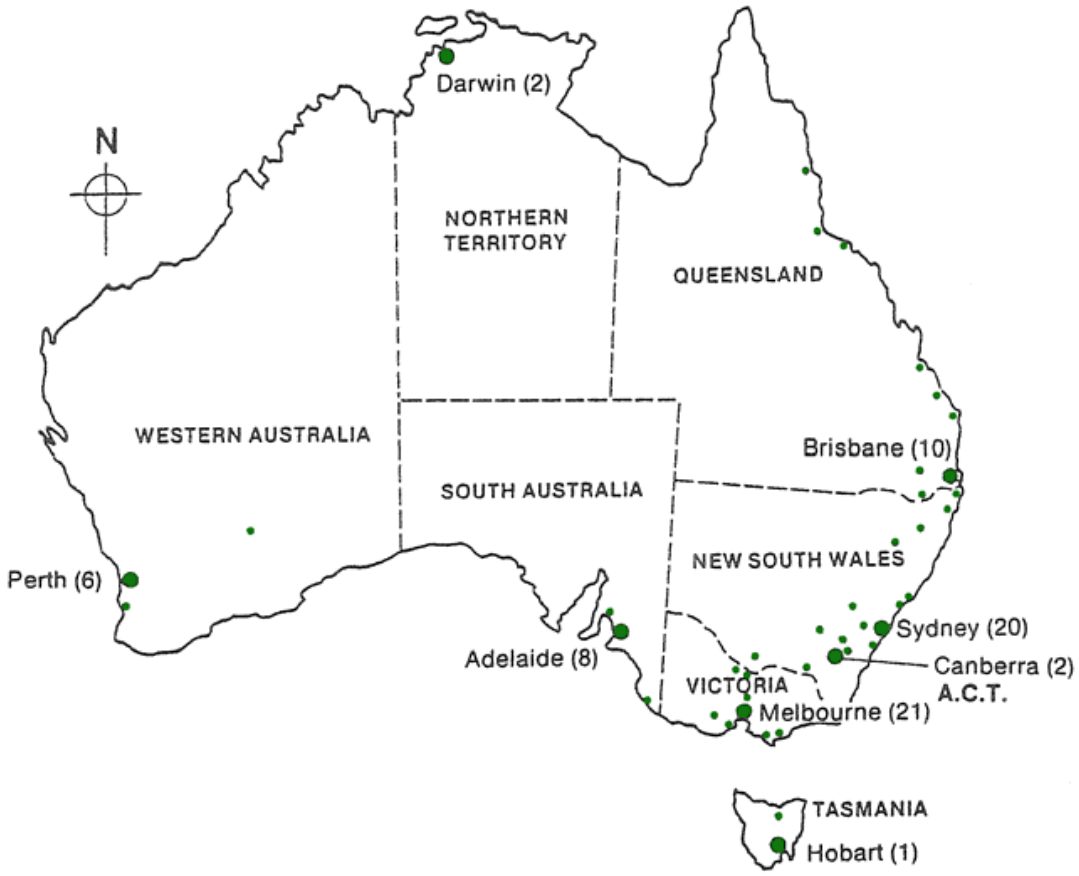


Figure 2-1. Distribution of schools participating in the 1985 Australian School Health and Fitness Survey indicated by the green dots.

2.2.2. Measurements

In the 1985 ASHFS, measurements included a wide range of health, lifestyle, physical fitness and biological parameters. Height, weight, waist circumference, short/long run, sit ups and blood pressure were measured in all children. Children aged 9-15 years old (n=6,559) completed a 36-item questionnaire on demographics, diet and physical activity in small supervised groups. Children aged 7-8 years (n=1,939) were thought to be too young to answer the questionnaire reliably so they were not asked to complete it. Data on parental education, country of birth, smoking and exercise were reported by children. Socio-economic status based on residential postcodes was derived using the Australian Bureau of Statistics Index of Relative Socioeconomic Disadvantage that was constructed using information from the Australian population census in 1981 [168]. Children aged 10 to 15 completed a 24-hour food

record. A 24-hour record is not considered a measure of usual intake and the method used to collect the dietary data in childhood was different to the methods used in adulthood (food frequency questionnaire, food habits questionnaire and a meal patterns chart). Skinfolds (biceps, triceps, subscapular and suprailiac), fasting blood samples, cardiorespiratory fitness tests were only done on children aged 9, 12 and 15 years. All measurements were done in clinics by trained field staff. Blood samples were taken by qualified nurses.

2.3. The Childhood Determinants of Adult Health (CDAH) study

There have been two completed follow up studies of the ASHFS participants in 2004-06 (CDAH-1) and 2009-11 (CDAH-2). The 2004-06 follow-up included measures of cardio-metabolic risk factors, mental health, demographic and other measures. The 2009-11 focused on life-stage transitions, depression, cardio-metabolic risk factors, and other covariates. There is a third adult follow-up currently being completed (CDAH-3). This thesis uses data from CDAH-1 and CDAH-2.

Data for analyses presented in chapters 3-7 was from the CDAH study involving follow-up of participants in the 1985 ASHFS. The CDAH study has both cross-sectional and longitudinal elements investigating the natural history of cardio-metabolic outcomes and other health outcomes. In the first follow-up of ASHFS participants (CDAH-1) in 2004-06, of total 5,170 individuals successfully traced and agreed to participate in the follow-up, 2,863 participants (55.4% of those enrolled) completed questionnaires (including the food frequency questionnaire) and reported on their alcohol drink status. A further 2,410 participants (47% of those enrolled) attended study clinics and completed additional questionnaires and extensive physical measurements including blood sampling. Another sub-sample of participants was asked and completed the Composite International Diagnostic Interview (CIDI) to provide information on lifetime and 12-month DSM-IV diagnoses for mental health. Of those, 2,193 participants completed the CIDI and reported on alcohol drink in the CDAH-1. At the follow-up 2 in 2009-10 (CDAH-2), of total participants continuously traced and involved, 2,960 people reported on alcohol consumption status, around 75% of CDAH clinic and CIDI attendees at the first follow-up participated in the second follow-up. Details of available data on alcohol consumption and alcohol-related outcomes were summarised in Figure 2-2.

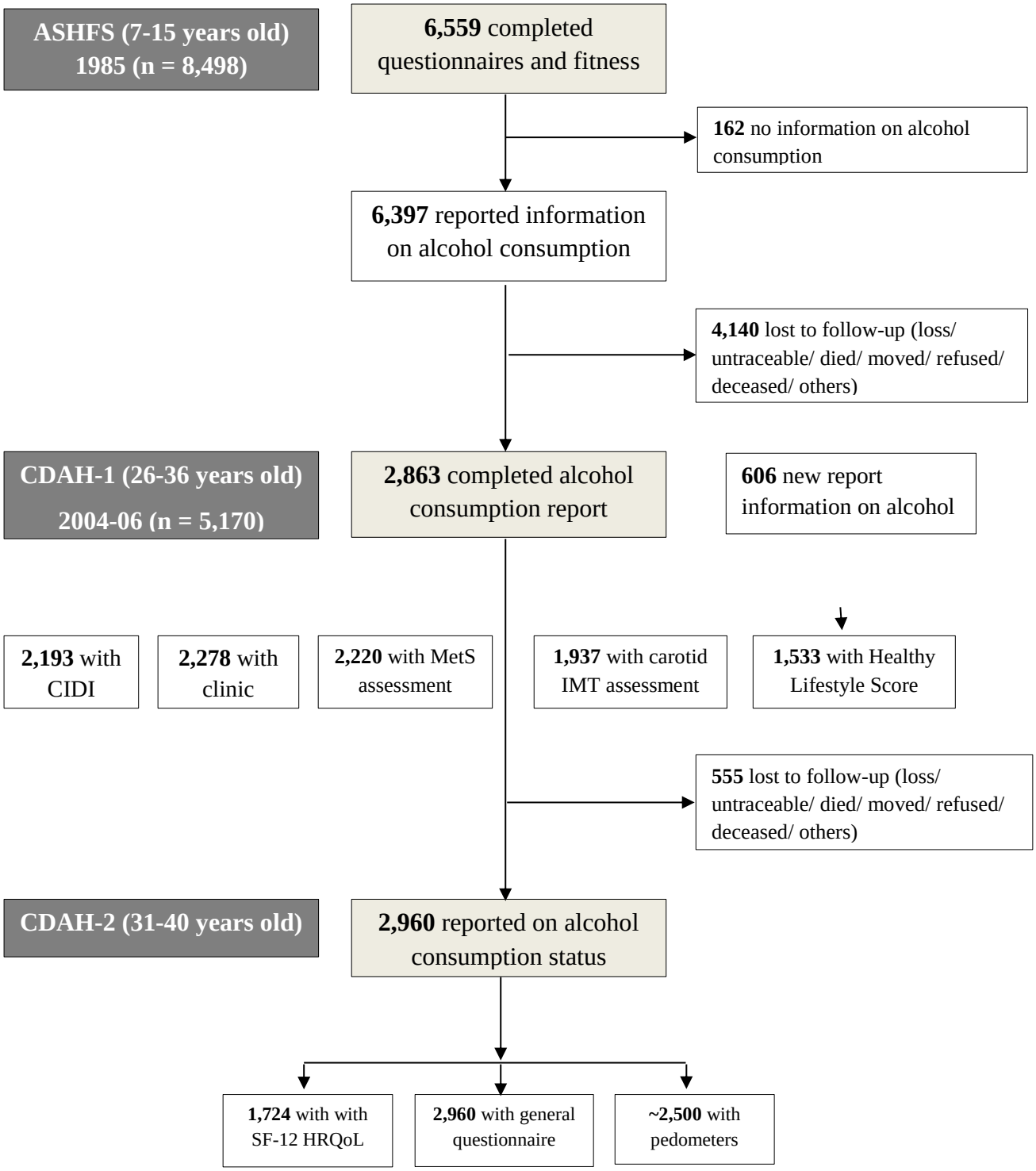


Figure 2-2. Flow chart of alcohol consumption status and alcohol-related outcomes during follow-up periods

2.3.1. CDAH-1 (2004-06)

2.3.2.1.Participants

During 2001–04, 80.5% (6,840/8,498) of the original participants were traced through the Australian Electoral Commission and the Australian National Death Index, and through school and family networks. Of these, 5,170 (60.8% of the original participants) agreed to enrol in the CDAH study, and 2,410 (28.4% of the original participants) attended one of the 34 clinics held across Australia during 2004–06. and completed additional questionnaires and extensive physical measurements including blood sampling. A further 1,524 participants (29% of those enrolled) completed additional questionnaires but did not attend a clinic. Study clinic locations were selected to maximize the proportion of enrolled participants living within a 10-kilometre radius and were attended by 55% of enrolees living within this distance. All participants provided written informed consent and the study was approved by the Southern Tasmania Health and Medical Human Research Ethics Committee.

A comparison of the CDAH clinic sample (n=2,410) with population data for Australian adults aged 25-34 [169, 170] shows that the proportions of CDAH participants living in each State and Territory are very similar to the general population. CDAH clinic participants were more likely than young adults in the general population to be tertiary educated (29.9% vs. 22.3%) and married (49.7% of men vs. 40.1%, 56.5% of women vs. 49.8%). A comparison of self-reported heights and weights in the CDAH sample with findings from the National Health Survey [171] show that CDAH participants were somewhat less likely to be obese (13% vs. 17% of males, 10% vs. 13% of females). Similar proportions were overweight (42% vs. 41% of males, 19% vs. 22% of females).

2.3.2.2.Study clinics

Clinics were held during 2004–06 in each state and territory of Australia, including New South Wales/Australian Capital Territory (nine clinics, 720 participants), Victoria (eight clinics, 705 participants), Queensland (eight clinics, 497 participants), Western Australia (three clinics, 205 participants), South Australia (three clinics, 190 participants), Tasmania (two clinics, 55 participants) and Northern Territory (one clinic, 38 participants). The clinic locations were chosen to maximise the proportion of enrolled participants living within a 10 km radius. These locations included community centres, schools, church halls or similar venues.

Two weeks before the clinic, participants were sent three questionnaires (general, diet and physical activity). They were asked to complete the questionnaires and bring them to the clinic. The data collection teams included ten data collectors, one field co-ordinator and a trained venipuncturist. Training for each test was provided by the same person for each state and territory. Clinics took approximately three hours to complete. Participants were required to fast for 12 hours before their clinic appointment. At the clinic, anthropometric measurements, blood pressure, vascular ultrasound examination and blood test were done before participants were provided breakfast. After breakfast, participants completed other examinations including cardiorespiratory fitness and muscular strength and were issued a pedometer. Those participants who enrolled in the CDAH study but refused or were unable to attend a clinic (n=2,760) were asked to complete a full or short questionnaire or visit local pathology centre for a blood collection. Because full data are not available for these participants, they were not included in the analyses used for this thesis.

2.3.2.3.Measurements

A summary of measurements already collected at baseline in 1985 and at follow-up 1 is presented in Table 2-1.

Table 2-1. Summary of data already collected in the CDAH study at baseline (1985) and twenty years later (2004-6)

	Measured in 1985 aged 7-15 (n=8,498)	**Measured at follow-up 2004-06** aged 26-36 (n=2,410‡ to 3,934)
Cardio-metabolic risk measures	Physical activity (questionnaire), diet[#], smoking, alcohol, anthropometry (height, weight, girths, skin folds), fitness, blood pressure[*], lung function[*], fasting blood lipids[*] (total cholesterol, HDL-cholesterol, triglycerides).	Physical activity (questionnaire and pedometer), diet, smoking, alcohol, anthropometry (height, weight, girths, skin folds), fitness, blood pressure, lung function, fasting blood biochemistry (glucose, insulin, total cholesterol, HDL and LDL-cholesterol, triglycerides, C-reactive protein, sex-hormone binding globulin, total testosterone), DNA, ultrasound measures of carotid intima-

		media thickness, brachial artery flow-mediated dilatation, left ventricular mass.
Mental Health	Bradburn Affect Scale [172]	CIDI-Auto
Demographic & other measures	Demographic characteristics, academic performance, attitudes to physical activity, health knowledge and beliefs, parental physical activity and smoking, self-reported health status, school type, size and PE/sport policies, activities and facilities.	Demographic characteristics (marital status, education, employment), self-reported health status (SF-12) and medication use, family history of heart disease and diabetes, self-reported birth weight, social support, personality type, women's reproductive health (menstrual characteristics, births).

‡ Clinic measurements in 2,410 participants, questionnaires in 3,934 participants; *measured in 9, 12 and 15-year-olds; # measured in 10 to 15-year-olds

Clinic Measures

Anthropometric measurements

For all anthropometric measurements participants were standing and dressed in light clothing without shoes. Participants were asked to remove outer layers of clothing, tight garments intended to alter body shape (such as corsets, lycra body suits and support tights), belts and heavy items from their pockets. Measurements were taken by trained staff following standardised protocols. All staff were trained by the same qualified anthropometrist. In total, seven staff took the anthropometric measurements. Halfway through the clinics in each state and territory, the trainer attended a clinic to check technique. Anthropometric measures were not taken on pregnant women (n=78).

Waist circumference

Waist circumference was measured three times over light clothing at the narrowest point between the lower costal border (10th rib) and the iliac crest, at the end of normal expiration. Measurements were taken using a Lufkin steel (non-stretch) tape measure and were recorded to the nearest 0.5cm. If the first two measurements were the same, a third measurement was not taken. Mean waist circumference was calculated.

Weight

Body weight was measured using a Heine portable scale (Heine, Dover, NH, USA) and recorded to the nearest 0.1kg. The scales were calibrated by an external calibration service before the first clinic in New South Wales, Australian Capital Territory, Western Australia and Victoria.

Height

Height was measured to the nearest 0.1cm using a portable Leicester stadiometer (Invicta, Leicester, UK). The head was held in the Frankfort horizontal plane and any obstructive headwear was removed.

Body mass index

Body mass index (BMI) was calculated from height and weight using the equation weight (kg) / height $(m)^2$. Overweight was defined as BMI ≥25.0-29.9kg/m2 and obese was defined as ≥30kg/m^2.

Blood pressure

Blood pressure was measured supine during the ultrasound examination using an Omron M4 Digital Automatic Blood Pressure Monitor (Omron Corporation, Kyoto, Japan). A correct cuff for the right upper arm was chosen before measurements. A mean of two readings, which were measured at least one minute apart, was used for analysis.

Blood biochemistry

A 30ml fasting blood sample was collected from the antecubital vein after an eight hour fast by a trained venipuncturist. Samples were collected into white-top (serum gel) vacutainer tubes for lipid and insulin analysis and grey-top (fluoride additive) vacutainer tubes for glucose.

The serum sample was used to measure lipids and insulin and the plasma sample was used to measure glucose. Triglycerides, total cholesterol, HDL cholesterol and glucose were analysed enzymatically on an Olympus AU5400 Mira plus autoanalyser (Olympus Optical, Tokyo, Japan). Fasting plasma insulin was measured by micropartical enzyme immunoassay kit

(AxSYM, Abbot Laboratories, Abbot Park, Illinois, USA) or electrochemiluminescence immunoassay (Elecsys Modular Analytics E170, Roche diagnostics, Mannheim, Switzerland). Homeostasis model assessment (HOMA) index was used to estimate insulin resistance.

Carotid intima-media thickness (IMT)

B-mode ultrasound studies of the left common carotid artery were performed using a portable Acuson Cypress (Siemens Medical Solutions USA Inc., Mountainview, CA) ultrasound machine with a 7.0 MHz linear-array transducer. Because the nature of clinical data collection for the CDAH study required an ultrasound machine to be moved around 34 clinics across Australia during 2004–06, the Acuson Cypress was identified as the only suitable portable system that incorporated ECG monitoring (necessary to ensure vascular measurements were collected at standardised phases in the cardiac cycle). All the ultrasound examinations were done by a single technician who travelled to each of the clinics.

Alcohol consumption

Standard drink

A standard drink in this thesis is defined as corresponding to 10 grams of pure alcohol (equivalent to 12.5 mL of pure alcohol) and was defined as a glass of wine, a bottle of beer or a shot of spirits [173] (Table 2-2). This definition has been used commonly in several Australian guidelines to reduce health risks from drinking alcohol [14, 174]. In Australia, all bottles, cans and casks containing alcoholic beverages are required by law to state on the label the approximate number of standard drinks they contain.

Table 2-2. Numbers of Australian standard drinks in common containers of various alcohol beverages [14]

Alcoholic beverage	Standard drinks
Low strength beer (2.7% alcohol)	
1 can or stubbie	0.8 standard drinks
285 mL glass	0.6 standard drinks
425 mL glass	0.9 standard drinks
slab of 24x375 mL cans or stubbies	19 standard drinks
Mid strength beer light beer (3.5% alcohol)	
1 can or stubbie	1 standard drinks
285 mL glass	0.8 standard drinks
425 mL glass	1.2 standard drinks
slab of 24x375 mL cans or stubbies	24 standard drinks
Full strength beer (4.9% alcohol) (includes diet beer)	
1 can or stubbie	1.4 standard drinks
285 mL glass	1.1 standard drinks
425 mL glass	1.6 standard drinks
slab of 24x375 mL cans or stubbies	34 standard drinks
Wine (9.5%-13% alcohol)	
100 mL glass	1 standard drink
Average restaurant serving (150 mL)	1.4-1.6 standard drinks
750 mL bottle	7 to 8 standard drinks
4-litre cask	36 to 43 standard drinks
Spirits (37%-40%)	
1 nip (30 mL)	1 standard drink
700 mL bottle	22 standard drinks
Pre-mixed spirits (5%-7% alcohol)	

1 can (375 mL)	1.5-2.1 standard drinks
1 bottle (275 mL)	1.1-1.5 standard drinks

Frequency and quantity of alcohol consumption

The frequency of consumption of nine alcoholic beverages from the food frequency questionnaire (FFQ) and their average alcohol concentration was used to estimate the number of standard drinks (10 grams of alcohol) consumed per week.

Each participant was asked to report his or her frequency of intake (options: never or <1/month, 1–3 times/month, once/week, 2–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–5 times/day, and >6 times/day) of beverages over the last 12 months for each type of alcoholic beverage consumed, from among beer, light beer, red wine, white wine/champagne, wine cooler, spirits, spirit-based mixed drinks, sherry/port, and other (e.g. cider) to estimate total alcohol intake. Overall, based on average number of times consumed in the last 12 months, alcohol intake was converted into total amount of alcohol consumed per week (grams/week) and total amount of alcohol consumed per day (grams/day). The total amount of alcohol consumed per week was calculated based on the average frequency and quantity consumed. It was determined by multiplying the number of drinking days per week by the estimated number of units consumed on drinking day for each beverage type, then summarising up of those amounts. The results were then also divided to get the total amount of alcohol consumed per day and converted to the corresponding standard drinks (i.e. total drinks per day (drinks/day) and total drinks per week (drinks/week). Individuals were classified into five groups according to daily alcohol intake: 0 drinks/day (non-drinkers), >0–1 drink/day (light drinkers), >1–2 drinks/day (moderate drinkers), >2–3 drinks/day (heavy drinkers) and >3 drinks/day (very heavy drinkers) based on Australian guidelines for low-risk drinking [14].

Alcohol use disorders

A sub-sample of 2,170 participants (97.7% of the total sample) had a 12-month DSM-IV-based AUDs diagnosis (e.g. alcohol dependence and/or alcohol abuse) obtained from the Composite International Diagnostic Interview (CIDI) [175], on a lap-top computer at the clinics. A recent review of computerized diagnostic instruments (including Australian studies using the CIDI) highlighted their reliability, comprehensiveness, and lower bias in comparison to routine clinical interviews [176]. The lifetime version of the CIDI will be used

which provides both lifetime and 12-month DSM-IV diagnoses, in addition to age of first symptom onset to inform temporal sequencing with our other variables. Interviewer training has been sourced from the WHO CIDI Australasian Training and Resource Centre (WHO-CIDI ATRC, Monash University).

Covariates

Demographics

Demographic variables were self-reported and obtained from the general questionnaire. Socioeconomic status was estimated using information on education and occupation. The highest level of education was assessed using the question "What is the highest level of education you have completed?" and was collapsed into three categories for analysis: school only (primary school, Year 7, 8, or 9 or equivalent, Year 10 or equivalent, Year 11 or equivalent, Year 12 or equivalent), vocational (trade/apprenticeship, certificate/diploma), university (university degree, higher university degree). Occupation was determined using the question "What is your main occupation now?" and gave examples for each of the categories. The answers were collapsed into four categories: professional/manager (manager or administrator, professional, associate professional), non-manual (tradesperson or related worker, advanced clerical or service worker, intermediate clerical, sales or service worker), manual (intermediate production or transport worker, elementary clerical, sales or service worker, labourer or related worker) and not in the workforce (no paid job). Marital status was determined using the question "What is your current marital status?" Response options were "single", "married", "de facto (living as married)", "separated/divorced", "widowed" and "other (please specify)". Parity was defined for women from the question "How many live births have you had?"

Smoking

Smoking status was classified as never, former or current smoker based on the two questions "Over your lifetime, have you smoked at least 100 cigarettes, or similar amount of tobacco?" and "How often do you now smoke cigarettes, cigars, pipes or any other tobacco products? Response options were "daily", "at least once per week (but not daily)", "less often than weekly" and "not at all".

Dietary intake

Food intakes and dietary habits were assessed using a FFQ. Participants completed a self-administered FFQ which included 127 food and beverages. Participants were asked to report how many times in the previous 12 months they had consumed each item. There were nine response options ranging from "never or less than once a month" to "6+ times per day". These categories have been widely used in FFQs, including the Nurses Cohort Study in the United States (3, 4) [177, 178]. The questionnaire did not ask about serving sizes and therefore a value for energy intake and other nutrients is not available. The FFQ was a modified version of the one used in the 1995 National Nutrition Survey [179] which was based on an existing FFQ developed for Australian populations [180].

Physical activity

Physical activity was measured using the long version of the International Physical Activity Questionnaire (IPAQ) [181]. The IPAQ assesses frequency, duration and intensity of physical activity. Participants were asked to report the number of days in the previous week they had done each activity for more than 10 minutes at a time, and how long they would usually spend doing each activity. The reliability and validity of the IPAQ has been tested in 12 countries including Australia [181]. Test-retest repeatability was assessed within the same week and showed good reliability (pooled coefficient of 0.81). Comparison with accelerometer data showed comparative validity (pooled Spearmans coefficient of 0.33) [181].

Cardiorespiratory fitness

Cardiorespiratory fitness was estimated as physical work capacity at a heart rate of 170 bpm (PWC_{170}). PWC_{170} was estimated using a bicycle ergometer (Monark Exercise AB, Vansbro, Sweden) pedaled at 60 rpm [182]. Participants pedaled continuously for 12 minutes at 60 rpm, which included three 4-minute periods where workload was increased at the end of every fourth minute. The workload increases were regulated so that heart rate achieved by the participants at the end of the first, the second, and the third period were greater than 115, 130 and 145 respectively. Steady state heart rate was recorded in the last 15 seconds of each period. Heart rate measurements were then plotted against mechanical power, and the data points were used to extrapolate to heart rate 170 bpm where the corresponding power estimate would represent the PWC_{170}. The greater values of PWC_{170} mean greater fitness. Because the

absolute workload achieved is a function of muscle mass [183], cardiorespiratory fitness was calculated as PWC_{170} adjusted for lean body mass to create an index uncorrelated with lean body mass. Participants with the following conditions were excluded from the test: body weight greater than 160 kg, being pregnant for more than three months, having current or past severe injuries or having hip or knee replacement, having resting blood pressure greater than 180 mmHg or having resting heart rate greater than 100 bpm. Of the 2410 participants attending clinic, 1960 (81.3%) completed this test.

Personality type

Personality type was measured at follow-up 1 using the NEO-FFI [184], a 60-item instrument that measures the five major domains of personality. Because this is a relatively fixed characteristic throughout life, we did not repeat this measure at the second follow-up.

2.3.2. CDAH-2 (2009-11)

2.3.2.1.Participants

During 2009–10, participants who assessments were undertaken in 2004-06 were traced and follow-up. The eligible sample at baseline (n = 3,965) comprised people who completed questionnaires about their health behaviours and outcomes, with a subset of these also having physical measures of the cardiovascular health in clinics (n = 2,385). At this second follow-up, assessments were only by questionnaire with 2,815 of the eligible sample at baseline completing these. The specific numbers with the data points relevant for this study are given in Figure 2-2.

Participants were invited to complete (a) a postal questionnaire, and (b) a computer-assisted telephone interview (CATI). Participants who wore and returned a pedometer at follow-up 1 (most clinic attenders) were asked to wear a pedometer again at follow-up2 for 7 days and record their daily steps. The CATI was of approximately 20 minutes duration and was needed to administer the mental health interview. Individuals who were not willing to complete the postal questionnaire or who did not return it after one written or telephone reminder were offered a short CATI, also of approximately 20 minutes duration.

A comparison of self-reported heights and weights in the CDAH sample at the follow-up 2 with findings from the National Health Survey for Australian population aged 25-44 [171] show that CDAH participants were somewhat less likely to be overweight/obese (50% vs.

60%) and current smokers (13% vs. 22%), and more likely to meet guidelines for physical activity (63% vs. 46%) than young adults in the general population.

2.3.2.2.Measurements

At follow-up 2 in 2009-10 the following data were collected.

Life-stage transitions

The questionnaire updated information on participants' highest level of education achieved, their occupation and employment status, marital status, living arrangements (parental home, cohabiting with partner etc) and number of children. The timing of transitions that have occurred since follow-up 1 was recorded.

Depression

Participants were again asked to complete the CIDI 3.0 [175], this time as a telephone interview restricted to the mood (depression, dysthymia) and anxiety (panic, agoraphobia, social phobia, generalized anxiety) disorder modules (At follow-up 1, participants completed the CIDI-Auto on a lap-top computer at the clinics). This fully structured diagnostic instrument was developed for use by trained non-clinical interviewers in diverse community populations. A recent review of computerized diagnostic instruments (including Australian studies using the CIDI) highlighted their reliability, comprehensiveness, and lower bias in comparison to routine clinical interviews [176]. The lifetime version of the CIDI was used which provides both lifetime and 12-month DSM-IV diagnoses, in addition to age of first symptom onset to inform temporal sequencing with our other variables. Depression and anxiety diagnoses over the lifetime and past 12 months showed good concordance with clinical assessments in a recent international study [175]. Interviewer training has been sourced from the WHO CIDI Australasian Training and Resource Centre (WHO-CIDI ATRC, Monash University).

Cardio-metabolic risk factors

Body composition

Participants were asked to self-report their weight. We had previously measured height and weight and determined the difference between objectively measured and self-reported height and weight in a large sample (n=1,185) of CDAH participants who attended study clinics at follow-up 1. We applied a correction factor to self-reported weights at follow-up as reported previously [185]. The agreement between self-reported and clinic BMI categories was high (κ=0.80 for males, κ=0.82 for females) but the error in self-reported BMI increased with increasing measured BMI, especially for women.

Alcohol consumption

Alcohol consumption was derived from the FFQ as for follow-up 1. We also administered the Rapid Alcohol Problem Screener – Quantity/Frequency (RAPS4-QF) to screen for alcohol use disorders [186]. This instrument had good sensitivity (86%) and specificity (95%) against DSM-IV alcohol dependence diagnosed with the CIDI in a population-based sample [187].

Physical activity

As for follow-up 1, we administered the International Physical Activity Questionnaire (IPAQ) [188], repeated additional questions about sedentary behaviour, and asked participants to wear a Yamax pedometer for 7 days. The IPAQ-long assessed the frequency, duration and intensity of moderate and vigorous intensity leisure, work, active commuting and yard/household physical activity in the past week. The measurement properties of the IPAQ have been assessed across 12 countries [189] and have been found to have very good levels of repeatability and fair to moderate validity when compared with data from accelerometers[189]. Pedometers have shown evidence of reliability and convergent and discriminative validity [190]. Yamax Digiwalker pedometers have been shown to be the most accurate and reliable pedometers available [191].

Smoking

Smoking was measured as per follow-up 1, including age started, quit attempts (timing/frequency), amount smoked per day. In addition, we administered the Fagerstrom Test for Nicotine Dependence (6 items) [192] and the Heavy Smoking Index (4 items) [193].

Diet

Diet was assessed using a FFQ assessing usual frequency of intake of food and beverages over the last 12 months developed for use with Australian adults and used in the 1st follow-up [194].

Other covariates

We measured other covariates that were potential effect modifiers or confounders of the associations between life-stage transitions and depression with cardio-metabolic risk.

Life-events were determined using a version of the List of Threatening Experiences adapted for use over a 5-year recall period [195].

Job strain was measured using validated instruments including the effort-reward imbalance scale (16 items) [196].

Social Support: We repeated the Index for Social Support, a 15 item instrument that was used at follow-up 1 [197].

Other health indicators: SF-12 was repeated [198] and participants were be asked to report their medication use and whether they or their first degree relatives had been diagnosed with cardiovascular disease or diabetes.

The short CATI

Participants who declined to complete the postal questionnaires or who did not return them after a written reminder were offered a short-CATI which collected the information above except that we measured physical activity with the IPAQ-short [188, 189] instead of the IPAQ-long, the short dietary questions on food habits concerning intake of fruits, vegetables, fish and fast food was also used [199], and we used the Kessler 10 depression questionnaire [200] instead of the CIDI. The K10 has good concordance with CIDI-generated depression and anxiety disorder diagnoses (AUC=0.90, 95% CI 0.89-0.91) [200].

Chapter 3

Associations between alcohol consumption and cardio-metabolic risk factors in young adults

Published in the journal

European Journal of Preventive Cardiology 2017; 24:1967-78.

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3 Chapter 3. Associations between alcohol consumption and cardio-metabolic risk factors in young adults

3.1. Introduction

There have been concerns that the apparent beneficial effects of moderate alcohol consumption on health outcomes have been over-stated because of the use of abstainers as the reference group [79, 80]. The authors of a recent systematic review of studies investigating alcohol use and mortality suggested using occasional drinkers as the comparator instead of abstainers, because abstainers often include former drinkers and people who have stopped drinking owing to health issues, thus creating a bias that made light drinkers appear healthier in comparison [80]. A further issue with existing studies [112-114] is the limited control for the potential confounding effects of dietary intake, physical activity, CRF and mental health, which are strongly associated with alcohol consumption [74, 76] and cardio-metabolic risk factors [115].

There is a need for greater evidence on the effects of alcohol consumption on young adults' cardio-metabolic health as young adults are the most likely to drink alcohol at levels associated with long-term risk of harm [47], and cardiovascular diseases are often 'silent' in the young [201]. The effects of alcohol on individual cardiovascular and metabolic risk factors in young adults are inconclusive. Authors have reported that alcohol consumption is associated with risk factors such as blood pressure in a J-shaped association [202] or insulin sensitivity in a positive linear association [203] among studies focused on young adults. Other risk factors such as waist circumference, triglycerides or HDL-C have not been fully examined for their relationship with alcohol consumption in young adults.

Few investigators have examined the association between alcohol consumption and the overall profile of cardio-metabolic risk factors in young adults, for example with a combined indicator such as the presence of MetS. Most authors have focused on older individuals finding that alcohol consumption has a positive [132], negative [124, 125] or J-shaped relationship [113] with metabolic syndrome. The differing results could be due to several reasons including the focus on older individuals in whom the recall of alcohol consumption across the life course might be unreliable [116] and that co-morbid diseases may influence associations [79].

Studying the relationship between alcohol consumption and cardio-metabolic risk factors in younger populations is therefore important to provide more precise estimates of the relationship and to potentially improve health information related to alcohol consumption for younger people. We therefore investigated the relationship between alcohol consumption and MetS among a cohort of young Australian adults with consideration of a wide range of potential confounders.

3.2. Methods

3.2.1 Study population

This is a cross-sectional analysis of data collected from 26 to 36-year-olds from the 2004–2006 follow-up of the CDAH study that began as the 1985 ASHFS, which comprised a nationally representative sample of school children aged 7–15 years. A detailed description of the cohort has been published elsewhere [204]. The flow of participants from baseline to follow-up is described in Figure 3-1.

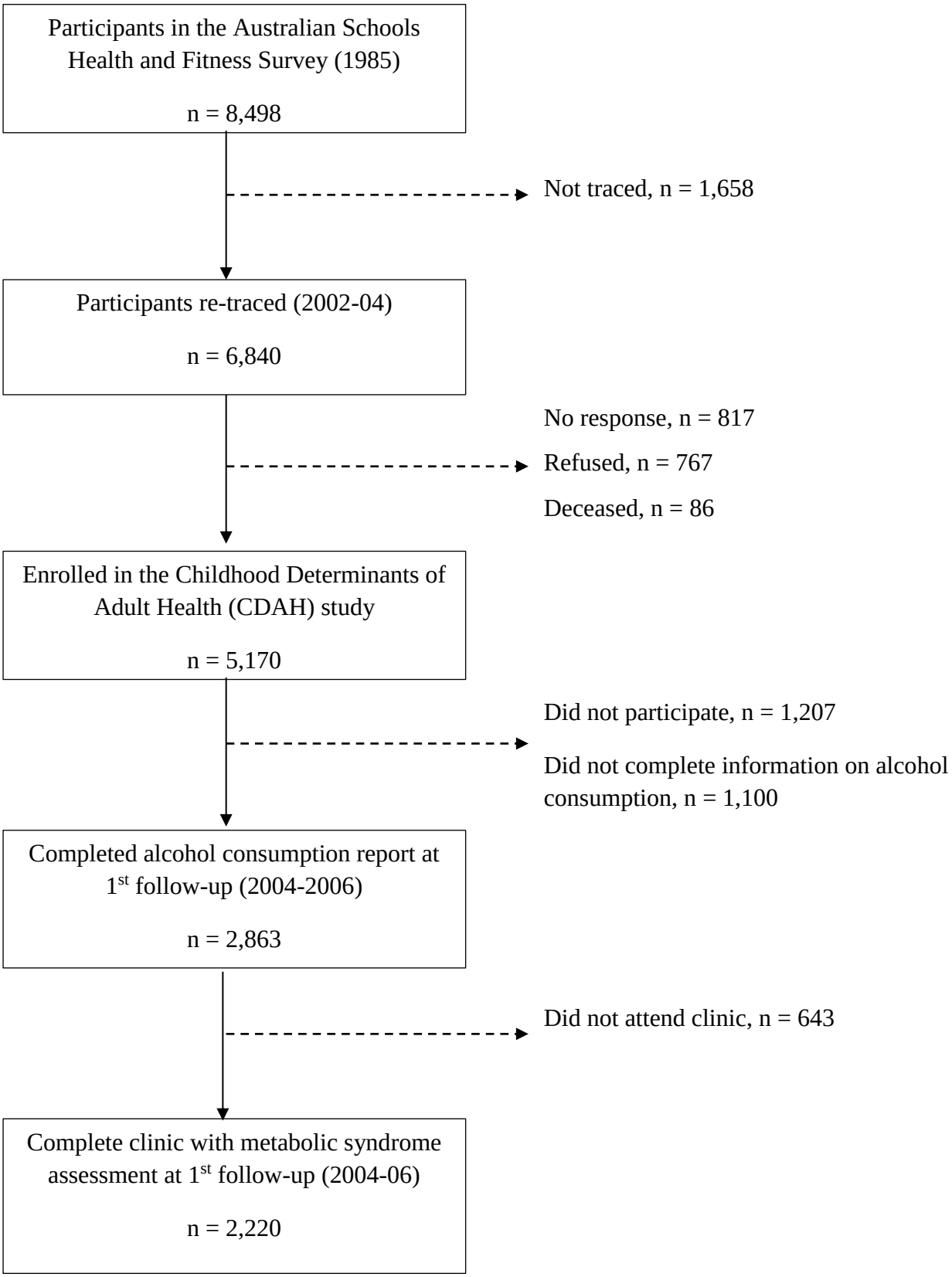


Figure 3-1. Flow chart of alcohol consumption status and alcohol-related outcomes during follow-up periods

3.2.2 Measurements

3.2.2.1. Alcohol consumption

We collected information regarding alcohol consumption using an FFQ. Each participant reported his or her frequency of intake (options: never or <1/month, 1–3 times/month, once/week, 2–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–5 times/day, and >6 times/day) of alcoholic beverages (options: light, medium or full strength beer; red, white and sparkling wine; wine cooler; spirits/liqueurs; spirit-based mixed drinks; sherry/port and other) over the last 12 months. The estimated amount of alcohol consumed per day for each type of beverage was determined by multiplying the frequency of drinking by the estimated grams of alcohol for each beverage type. The total amount of alcohol consumed per day was defined as the sum of the amount of alcohol consumed for each type of beverage [174].

Individuals were classified into five groups according to daily alcohol intake: 0 drinks/day (non-drinkers), >0–1 drink/day (light drinkers), >1–2 drinks/day (moderate drinkers), >2–3 drinks/day (heavy drinkers) and >3 drinks/day (very heavy drinkers) based on Australian guidelines [14]. Beer, wine and spirits were classified into three categories: 0 g/day, >0–10 g/day and >10 g/day). Further categorisation of the types of alcohol was not possible due to small numbers in higher consumption groups.

A sub-sample of 2,170 participants (97.7% of the total sample) had a 12-month DSM-IV-based AUDs diagnosis (e.g. alcohol dependence and/or alcohol abuse) obtained from the CIDI [205].

3.2.2.2. Cardio-metabolic risk factors

Height, weight and waist circumference were measured, and BMI was calculated. Fasting blood samples were used to measure serum triglycerides (mmol/L), total cholesterol, HDL-C (mmol/L) and fasting insulin (µIU/L) concentrations. Fasting plasma glucose (mmol/L) was measured enzymatically. Blood pressure (BP) was measured using a digital automatic monitor. A detailed description of the measurements is provided in the appendix.

3.2.2.3. Definition of metabolic syndrome

The primary outcome was MetS and its components as defined by the Adult Treatment Panel III of the National Cholesterol Education Program (NCEP/ATP-III) [206]. MetS is defined as

someone having three or more of the five risk factors: abdominal obesity (waist circumference >102 cm in men; >88 cm in women), hypertriglyceridemia (triglycerides ≥150 mg/dL), low level of HDL-C (i.e. <40 mg/dL (1.08 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women), high BP (≥135/85 mmHg) and high levels of fasting plasma glucose (i.e. ≥110 mg/dL (≥5.6 mmol/L). MetS was also expressed in a continuous MetS risk score, which was computed from weighted principle components and gender specific cut-offs as a continuous outcome, described in detail by Wijndaele et al [207]. The mean value was used in the analysis.

3.2.2.4. Covariates

The covariates and their measurements are described in full in the supplement. In brief, the following covariates were considered: age, sex, SES quartile based on area of residence, region of residence, education level, occupation, marital status and smoking status measured by questionnaires; physical activity determined by the international physical activity questionnaire (IPAQ) [181]; CRF estimated as physical work capacity (PWC) [182]; dietary intake assessed using a FFQ, and then derived as a Dietary Guideline Index (DGI) score; childhood alcohol consumption; health-related quality of life (HRQoL) (SF-12 physical and mental component scores), and depression and anxiety from the aforementioned CIDI [205].

3.2.3 Statistical analysis

We examined the association between alcohol consumption categories and dichotomous MetS using multivariable log binomial regression (prevalence ratios [PR] and 95% CIs), and with each individual cardio-metabolic risk factor using multivariable linear regression (predicted means values and/or β coefficients and 95% CIs). The light drinkers' group was chosen as the reference category. We also examined associations among beer, wine and spirits categorised as in the abovementioned section.

Potential covariates were included in the models in accordance with purposeful model building procedures [208]. Models are shown adjusted for socio-demographics including sex, age, region, SES, educational level, occupation and marital status (model 1); model 1 plus behavioural risk factors including smoking, dietary intake and physical activity (model 2); model 2 plus CRF (model 3); and model 3 plus mental health, i.e. depression and anxiety (model 4). Interaction terms between covariates and alcohol consumption were entered into final regression models to test the effect modification. There was no evidence of effect

modification by sex (see online Appendix material); therefore, the results for men and women are presented together.

The following sensitivity analyses were performed: (1) using the non-drinkers (abstainers) group as the reference category, (2) excluding participants who had been positively diagnosed for alcohol abuse or dependence, and (3) examining the effect of not participating in follow-up sessions. Multiple imputation (MI) using chained equations with 30 estimations was used to replace missing covariate data. Details are provided in the supplement. The threshold for significance was $p \leq 0.05$ (two-tailed). Analyses were performed with the Stata 12.0 software program.

3.3. Results

3.3.1. Characteristics of the study population

Of the 2,220 participants, the majority were light and moderate drinkers, while less were abstainers, heavy or very heavy drinkers who consumed alcohol daily (Table 3-1). Compared to light drinkers, non-drinkers were less often male, less likely to have reported drinking in childhood, less likely to be smokers at adulthood, had less AUDs in adulthood, had a higher DGI score, had lower physical and mental HRQoL, more often lived in a low SES postcode, were more often married, less physically active and had lower daily step counts. The overall prevalence of MetS was 7%. It was highest in non-drinkers (8%) and lowest in heavy drinkers (3%) (Table 3-2).

3.3.2. Association between alcohol consumption and individual cardio-metabolic risk factors

Individual multivariable models examining alcohol consumption and each risk factor are presented in the supplement (Table 3-3 to Table 3-8). In model 4, compared to light drinkers, non-drinkers had a significantly higher waist circumference (β=1.88 (0.41, 3.36), $p<0.05$) and lower HDL-C (β=-0.06 (-0.10, -0.01), $p<0.01$); moderate (β=0.09 (0.06, 0.13), $p<0.001$) and heavy drinkers (β=0.20 (0.14, 0.26), $p<0.001$) had significantly higher HDL-C; and very heavy drinkers had significantly higher SBP (β=3.01 (0.90, 5.12), $p<0.01$) and DBP (β=2.07 (0.33, 3.81), $p<0.05$) (Figure 3-2).

People who did not drink beer (0 g/day) had significantly higher waist circumference (β=1.46 (0.36, 2.55), p<0.01) and significantly lower HDL-C (β=-0.08 (-0.11, -0.05), p<0.001) than those who drank light amounts of beer (>0–10 g/day) (see Appendix Table 3-3 and Table 3-5). High consumption of wine (>10 g/day) was associated with a significantly higher SBP (β=2.40 (0.87, 3.94), p<0.01) and DBP (β=1.65 (0.39, 2.92), p<0.05) than those who only had a light consumption of wine (>0-10 g/day) in the fully adjusted models (see Appendix Table 3-6 and Table 3-7).

Table 3-1. General characteristics of participants according to alcohol consumption

		Total participants (n=2,220)	Non-drinkers (0 g/day) (n=292)	Light drinkers (>0-10g/day) (n=1,204)	Moderate drinkers (>10-20g/day) (n=486)	Heavy drinkers (>20-30 g/day) (n=116)	Very heavy drinkers (>30g/day) (n=122)	P_{value}
Sex, n (%)	Male	1,056(48)	92(32)	509(42)	295(61)	76(66)	84(69)	<0.001***
Age (years)	Mean (SD)	29.3(2.5)	29.5(2.4)	29.3(2.6)	29.2(2.5)	29.4(2.7)	29.6(2.6)	0.495
Region of residence (%)	Major cities	1,698(76)	203(69)	911(76)	399(82)	97(84)	88(72)	<0.01**
	Inner regional	346(16)	59(20)	199(16)	55(11)	13(11)	20(16)	
	Outer regional	158(7)	25(9)	83(7)	31(6)	5(4)	14(11)	
	Remote	17(1)	5(2)	10(1)	1(1)	1(1)	0(0)	
Education, n (%)	Tertiary	959(43)	115(39)	513(43)	228(47)	64(55)	39(32)	<0.05*
	Vocational	678(31)	97(33)	374(31)	130(27)	32(28)	45(37)	
	School only	578(26)	80(28)	314(26)	126(26)	20(17)	38(31)	
SES (Quartile base on area of residence), n (%)	Quartiles 1	493(22)	88(30)	275(23)	81(17)	15(13)	34(28)	<0.001***
	Quartiles 2	531(24)	73(25)	305(25)	102(21)	25(22)	26(21)	

		Total participants (n=2,220)	Non-drinkers (0 g/day) (n=292)	Light drinkers (>0-10g/day) (n=1,204)	Moderate drinkers (>10-20g/day) (n=486)	Heavy drinkers (>20-30 g/day) (n=116)	Very heavy drinkers (>30g/day) (n=122)	P_{value}
	Quartiles 3	557(25)	77(26)	293(24)	122(25)	35(30)	30(25)	
	Quartiles 4	638(29)	54(19)	330(28)	181(37)	41(35)	32(26)	
Occupation, n (%)	Professionals	1,196(55)	124(43)	633(53)	298(62)	81(71)	60(50)	<0.001***
	White collar	387(18)	58(20)	231(20)	75(16)	13(12)	10(8)	
	Blue collar	377(17)	36(12)	210(18)	77(16)	14(12)	40(34)	
	Unemployed	228(10)	72(25)	110(9)	30(6)	6(5)	10(8)	
Marital status, n (%)	Married/living as married	1,520(69)	214(73)	829(69)	322(66)	70(60)	85(70)	0.116
	Single	626(28)	68(23)	333(28)	150(31)	39(34)	36(29)	
	Divorced/ Separated	74(3)	10(3)	42(3)	14(3)	7(6)	1(1)	
Total alcohol consumed	gm/day	9.9(13.7)	--	4.6(2.7)	14.3(2.7)	24.3(2.9)	54.9(22.7)	<0.001***

		Total participants (n=2,220)	Non-drinkers (0 g/day) (n=292)	Light drinkers (>0-10g/day) (n=1,204)	Moderate drinkers (>10-20g/day) (n=486)	Heavy drinkers (>20-30 g/day) (n=116)	Very heavy drinkers (>30g/day) (n=122)	P_{value}
Total beer	gm/day	4.2(9.5)	--	1.5(2.0)	5.5(4.3)	9.9(5.7)	30.4(25.6)	<0.001***
Total wine	gm/day	4.1(7.6)	--	2.0(2.1)	6.4(4.7)	11.1(6.1)	18.8(23.8)	<0.001***
Total spirits	gm/day	1.6(3.5)	--	1.1(1.4)	2.4(2.9)	3.3(4.8)	5.6(10.8)	<0.001***
Total PA	mins/week	768(514)	689(518)	783(512)	751(496)	773(538)	881(542)	<0.01**
Daily steps	10,000 steps	0.9(0.3)	0.8(0.3)	0.9(0.3)	0.9(0.3)	0.9(0.3)	1.0(0.4)	<0.001***
PWC_{170}	Mean (SD)	0.3(35.3)	-8.7(32.6)	-1.2(33.9)	7.5(38.8)	5.0(35.5)	-0.3(35.0)	<0.001***
Dietary (DGI)	Mean (SD)	101(19)	101(20)	103(19)	100(18)	95(16)	83(16)	<0.001***
DGI excluding alcohol	Mean (SD)	92(19)	92(20)	94(19)	92(18)	88(17)	82(16)	<0.001***
Physical HRQoL	Mean (SD)	52.5(6.5)	51.2(8.1)	52.6(6.2)	52.9(6.2)	54.2(5.0)	52.6(6.3)	<0.001***
Mental HRQoL	Mean (SD)	49.8(8.8)	48.7(9.7)	50.0(8.5)	49.8(8.9)	49.7(8.6)	50.5(8.8)	0.225
AUDs prevalence, n (%)	Positive	253(12)	5(2)	84(8)	90(20)	30(28)	44(40)	<0.001***
Drink at childhood, n (%)	Positive	566(32)	58(24)	292(31)	137(36)	40(43)	39(39)	<0.01**

		Total participants (n=2,220)	Non-drinkers (0 g/day) (n=292)	Light drinkers (>0-10g/day) (n=1,204)	Moderate drinkers (>10-20g/day) (n=486)	Heavy drinkers (>20-30 g/day) (n=116)	Very heavy drinkers (>30g/day) (n=122)	P_{value}
Smoking prevalence, n (%)	Positive	490(22)	29(10)	239(20)	144(30)	34(30)	44(36)	<0.001***
Depression/anxiety, n (%)	Positive	321(16)	53(20)	181(16)	52(12)	20(18)	15(14)	<0.05*
History of CVD, n (%)	Positive	237(11)	29(10)	119(10)	51(11)	17(15)	21(18)	0.069

Data are shown as Number (Percentage) for categorical variables and as Mean (SD) for continuous variables.

SES, socioeconomic status; PA, physical activity; PWC_{170}, physical work capacity; DGI, Dietary Guideline Index; HRQoL, health-related quality of life; AUDs, Alcohol use disorders; CVD, Cardiovascular disease.

*P<0.05, **P<0.01, ***P<0.001

Table 3-2. Clinical characteristics of the study population according to alcohol consumption

	Alcohol consumed per day					
	Non-drinkers (0 g/day)	Light drinkers (>0-10g/day)	Moderate drinkers (>10-20g/day)	Heavy drinkers (>20-30 g/day)	Very heavy drinkers (>30g/day)	P_{value}
N (%)	292 (13)	1,204 (54)	486 (22)	116 (5)	122 (6)	
BMI (kg/m^2)	26.4±5.8	25.6±4.8	25.3±4.2	24.9±3.6	25.7±4.2	<0.05
Weight (kg)	76.0±19.6	75.8±16.7	77.5±16.9	77.9±14.2	79.9±16.7	<0.05
Waist circumference (cm)	84.6±14.3	83.0±12.2	83.8±12.0	83.8±10.8	85.7±10.7	0.094
Systolic BP (mmHg)	116±13	117±12	120±13	121±12	124±13	<0.001
Diastolic BP (mmHg)	72±10	72±9	72±10	74±8	76±11	<0.001
Triglyceride (mmol/l)	1.1±0.8	1.1±0.8	1.2±0.9	1.1±0.7	1.2±0.8	0.221
Total cholesterol (mmol/l)	4.8±1.0	4.9±1.0	4.9±1.0	5.0±1.0	5.0±1.0	0.376
HDL-C (mmol/l)	1.4±0.3	1.4±0.3	1.5±0.3	1.6±0.3	1.6±0.4	<0.001
LDL-C (mmol/l)	3.0±0.8	3.0±0.8	2.9±0.9	2.9±0.9	2.9±0.8	0.786
Fasting glucose (mmol/l)	4.9±0.6	5.0±0.4	5.0±0.4	5.1±0.4	5.1±0.5	<0.001
Fasting insulin (µU/ml)	7.8±5.7	7.2±4.6	6.5±4.0	6.3±3.3	6.0±3.9	<0.001
cMSy	0.2±0.8	0.1±0.7	-0.1±0.7	-0.2±0.6	-0.0±0.7	<0.001
MetS prevalence (%)	8	7	5	3	7	0.304
Central obesity (%)	23	14	9	8	11	<0.001
High triglycerides (%)	16	14	15	15	19	0.585
Low HDL-C %)	14	12	8	3	6	<0.001
High BP (%)	7	6	8	5	18	<0.001
High fasting glucose (%)	9	9	11	10	15	0.202

Data are shown as mean (± standard deviation) for continuous variables and number (percentage) for categorical variables.

BMI=body mass index; BP=blood pressure; HDL-C=high-density lipoprotein-cholesterol; LDL-C=low-density lipoprotein-cholesterol; MetS=metabolic syndrome; cMSy=continuous metabolic syndrome risk score.

*P<0.05, **P<0.01, ***P<0.001

Analyses using non-drinkers instead of light drinkers as the reference category made little difference to the findings (see Appendix Figure 3-4, Figure 3-5 and Table 3-22).

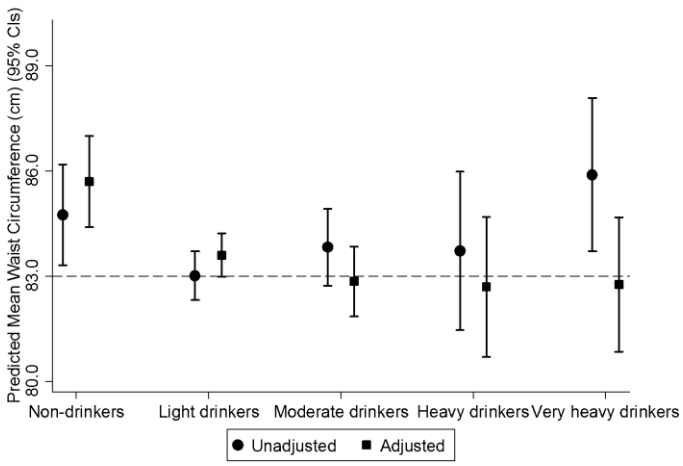
Sensitivity analyses excluding those with an AUD mostly strengthened the associations (Appendix Table 3-12). Applying inverse probability weights (IPWs) did not change the results (Appendix Table 3-14 to Table 3-19).

3.3.3. Association between alcohol consumption and metabolic syndrome

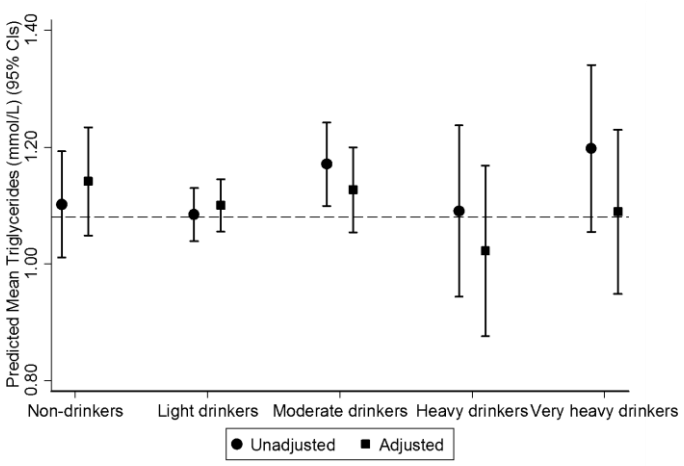
Compared to light drinkers, non-drinkers had a non-significantly higher prevalence of MetS, whereas moderate drinkers and heavy drinkers had a lower prevalence of MetS, and very heavy drinkers had a higher prevalence of MetS in unadjusted analyses (Figure 3-4, Table 3-9). Model 4 showed that only moderate drinkers had a significantly lower prevalence of MetS (PR=0.64 (0.41, 0.99), p<0.05) than that of light drinkers. Demographic factors including SES constituted most but insignificant modification (model 1), whereas other lifestyle and health behaviours including smoking, dietary intakes and physical activity accounted for significant change (model 2) compared to the unadjusted model. These results were not markedly changed in the two further adjusted models with CRF and mental health (Table 3-9).

The analyses using non-drinkers instead of light drinkers as the reference category made only modest difference in the findings (see Appendix Figure 3-5 and Table 3-23).

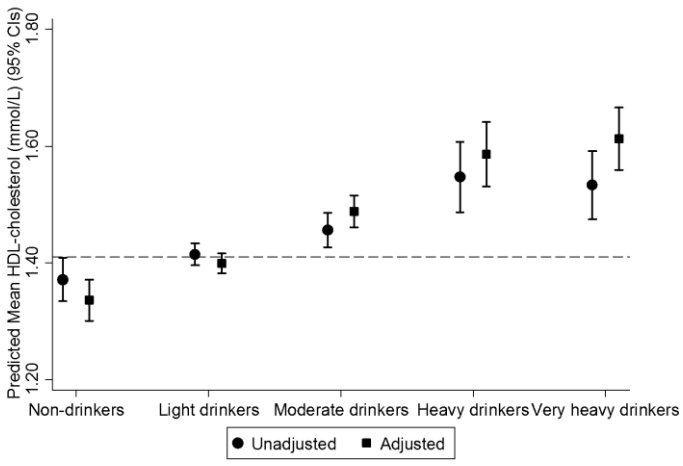
Beer, wine and spirits had different associations with the prevalence of MetS. There was a significantly higher prevalence of MetS in people who did not drink beer than those who drank light amounts of beer (PR=1.62 (1.14, 2.32), p<0.01), and in people who did not drink wine than those who drank small amounts of wine (PR=1.59 (1.12, 2.25), p<0.01) (see Table 3-7). Analyses that utilised the types of alcoholic beverage as continuous measures rather than categorical ones showed that there were no statistically significant associations between types of alcoholic beverages and prevalence of MetS (Appendix Table 3-11).



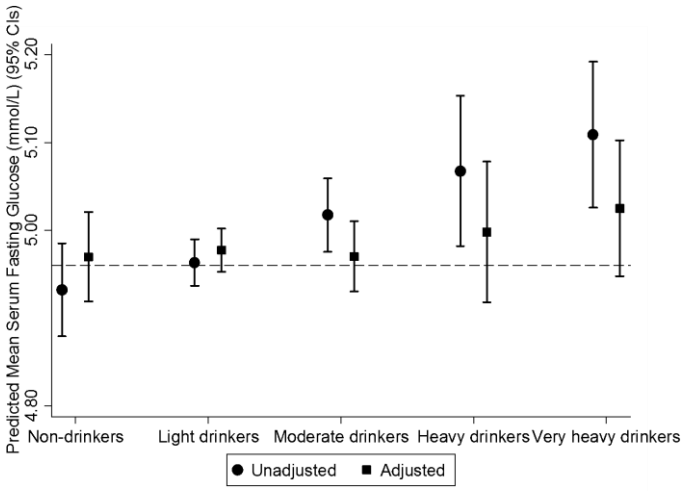
Waist circumference (A)



Serum Triglycerides (B)



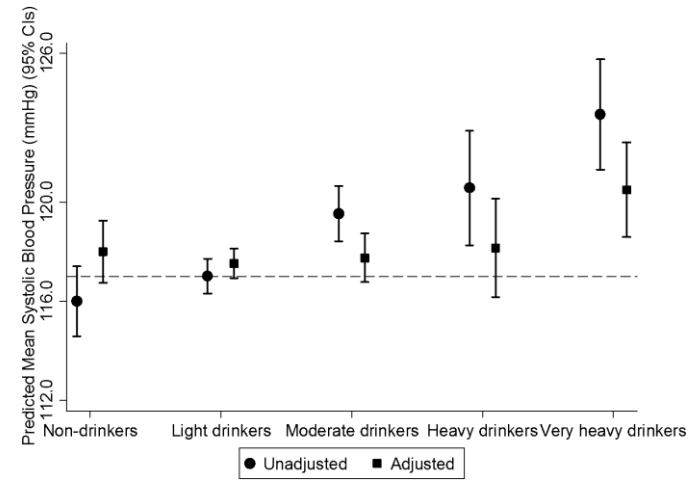
Serum HDL-cholesterol (C)



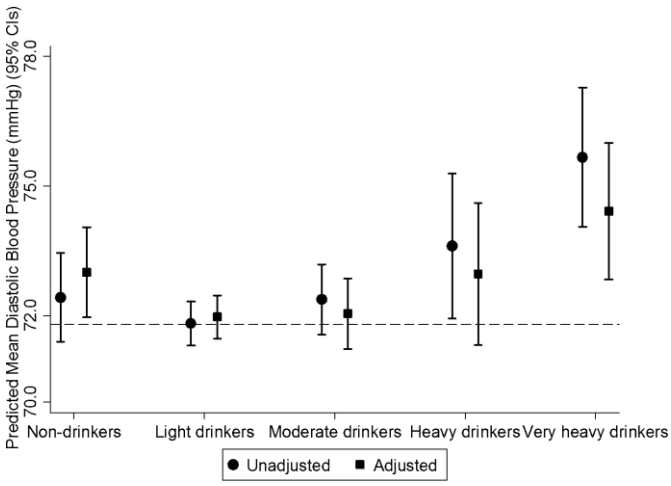
Fasting blood glucose (D)

Figure 3-2: Predicted means of waist circumference (A), triglycerides (B), HDL-cholesterol (C), and serum fasting blood glucose (D) according to alcohol consumption.

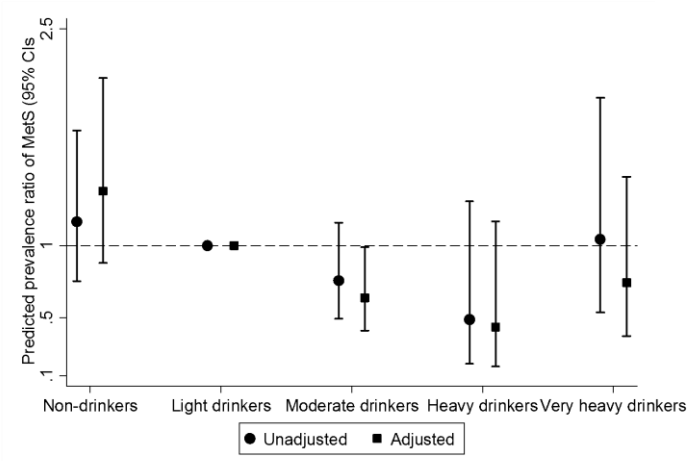
Bars represent 95% confidence intervals. Adjusted models include sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety. Details can be found in the Appendix, Table 3-3 to Table 3-10.



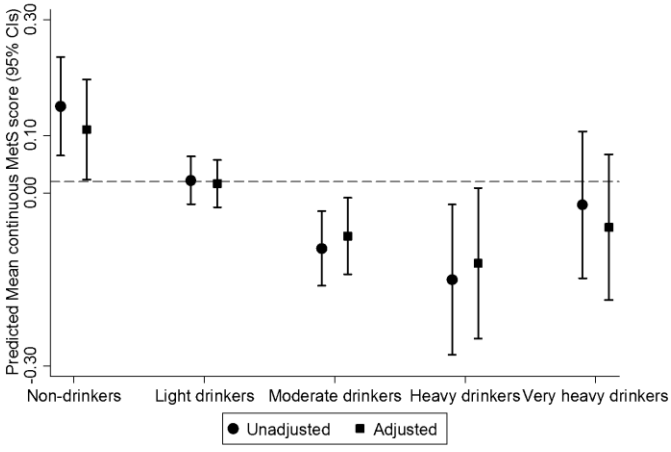
Systolic Blood Pressure (E)



Diastolic Blood Pressure (F)



Prevalence ratio of MetS (G)



Continuous MetS Risk Score (H)

Figure 3-3: Distribution of predicted means of systolic blood pressure (E) and diastolic blood pressure (F), prevalence ratio of MetS (G) and predicted mean value of continuous MetS risk score (H) according to alcohol consumption status.

Bars represent 95% confidence intervals. All models were adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety. Details can be found in the Appendix, Table 3-3 to Table 3-10.

Similar results were found when using non-drinkers instead of the light drinkers as the reference group. There was no evidence of interactions between alcohol and other variables in the final adjusted models. Sensitivity analyses showed similar associations after excluding those with an AUD (see Appendix Table 3-13). Applying IPWs made the results for the heavy drinkers somewhat stronger (Appendix Table 3-20).

Increasing levels of alcohol consumption were associated with a reduction in the continuous MetS risk score (see Figure 3-3 and Appendix Table 3-10). The association between higher levels of alcohol consumption and lower continuous MetS risk score were not significantly changed by further adjustment (see Figure 3-3 and Appendix Table 3-10).

3.4. Discussion

Our results suggested a lower burden of cardio-metabolic risk factors among moderate drinkers compared to light drinkers in this sample of young adults. Results were significant after adjusting for potential confounders, including physical activity, CRF and mental health that have not been explored in previous studies. There was evidence of higher SBP and DBP in those participants with very high alcohol consumption.

Our findings on the association between moderate alcohol consumption and lower MetS prevalence are consistent with the only other study focused on young adults [209] and some studies in populations with a wider age range [108, 113, 125]. However, the results are in contrast to other studies showing no association between alcohol drinking and MetS [124, 138] or that heavy drinking increased the risk of MetS [114]. Other health behaviours including smoking, dietary intake and physical activity were significantly associated with alcohol consumption and caused most of the change in the magnitude of the association between alcohol consumption and MetS in the adjusted models. This suggests that inadequate control for confounders might have led to an overestimation of the association between alcohol consumption and MetS in previous studies of young adults. In terms of the individual components of MetS, we found that increasing levels of alcohol consumption had a favourable association with HDL-C, whereas it was associated with higher levels of BP and waist circumference in young adults. The dose-dependent association of alcohol and HDL-C levels is among a limited finding observed in young adults, but it is consistent with a number of previous studies in populations with a wider age range [144, 210].

There were important differences between light drinkers and non-drinkers in this cohort of young adults. Non-drinkers had lower levels of physical activity, met fewer dietary guidelines, had poorer CRF and a higher prevalence of depression and/or anxiety but a lower prevalence of smoking compared to light drinkers. However, using non-drinkers instead of light drinkers as the reference group made only a modest difference to the associations. Using non-drinkers as the comparator was not problematic in this sample of young adults; however, the differences in the health profiles of non-drinkers versus drinkers supports the suggestions made by other researchers to use light drinkers as the reference category when studying alcohol and health markers.

A higher prevalence of MetS and higher mean continuous MetS risk scores were observed among non-beer and non-wine drinkers, but not non-spirit drinkers, compared to people that drink light amounts of these beverages. People that did not drink beer had significantly higher waist circumferences and lower HDL-C compared to those that drank light amounts of beer, whereas people that consumed greater amounts of wine had significantly higher SBP and DBP than those that drank lower levels of wine. Others have also suggested a lower prevalence of MetS in consumers of beer and wine, but not in those consuming spirits compared to non-drinkers [124, 211]. The analyses that used the types of alcoholic beverage as continuous measures rather than categorical measures in the present study showed that there were no statistically significant associations between types of alcoholic beverages and prevalence of MetS. These results indicated that alcohol consumption was associated with lower MetS only in those who consumed light to moderate amounts of beer or wine, but not irrespective of all types of beverages consumed. While most studies of the relationship between alcohol and cardio-metabolic health in young adults did not analyse the effect of beverage type, our results indicated that young adults who drank light amounts of beer and/or wine might have better health than those consuming higher amounts of these types or other types of alcohol.

The biological mechanisms relating alcohol consumption to each component of MetS are complex. Alcohol intake may increase HDL-C either by synthesis or clearance of HDL-C or by the effects on enzymes and proteins influencing HDL-C metabolism [212]. The association of very heavy drinking with higher BP is in agreement with one previous study in young adults and populations with a wider age range [146, 147]. Several possible mechanisms regarding the effects of alcohol consumption on BP have been proposed such as impacts on the central nervous system, sympathetic nervous system, renin-angiotensin system or aldosterone system [213, 214].

The apparent favourable association between wine, particularly red wine with its higher levels of bioflavonoids and antioxidant polyphenols, and cardiovascular health has also been reported in previous studies [215, 216]. In the present study, beer and wine showed similar relationships with cardio-metabolic risk factors, suggesting that the common components of these drinks, such as ethanol, account for the favourable effects. There remains the possibility that the associations are due to residual confounding. There are a number of factors associated with the type of alcohol consumed, such as SES, dietary intake, physical activity and fitness and cardio-metabolic risk factors that were not taken into consideration in previous studies. In our study, by taking these covariates into consideration, the favourable association between drinking wine and beer and cardio-metabolic health remained significant, although the magnitude was small.

Current guidelines recommend 'responsible alcohol consumption', i.e. no more than two standard drinks per day on average, to avoid health risks associated with drinking alcohol [14]. We found that most people in our cohort were consuming alcohol at or below this level. This suggests that current guidelines were mainly adhered to, at least in younger, somewhat higher SES adults similar to our cohort. Nonetheless, recent Australian data has revealed that people in their 40s are more likely to drink at lifetime risky levels than any other age group [47]. Therefore, health promotion messages should convey both the positive and negative effects on the cardio-metabolic and general health of young people.

The strengths of the present study include the large sample size that provided sufficient power to investigate our hypotheses. We considered a wide range of potential confounders previously unexplored in studies of young [203, 217] and even older [112, 130] populations, including depression and anxiety, CRF, physical activity and diet. Although each of these factors was strongly associated with levels of drinking, socio-demographic factors, smoking status, diet and physical activity were the main confounders of the association. The sample also provided sufficient factors allowing investigation of the associations across all levels of alcohol consumption. In particular, there were important differences between the very heavy drinking group and other groups in terms of outcomes and characteristics. Our young healthy sample with few co-morbid diseases and our ability to exclude those with AUDs, thus addressing potential issues with reverse causation is a strength of our study. There were also several limitations with the present study. The cross-sectional design means we were unable to examine casual associations between alcohol consumption and MetS. Misclassification of alcohol intake may have occurred due to the self-reporting aspect of the study. However, self-report recall methods have been reviewed to offer a reliable and valid approach to measuring

alcohol consumption. Self-reported alcohol intake has been shown to be significantly associated with GGT, which is a useful marker in the prediction of hypertension and CVD [20]. It is possible that the discrepancies between our findings and others are related to the measurement and classification of alcohol consumption. Authors use different methods to classify the type of alcoholic beverages. For example, Djousse et al. [124] identified alcohol categories of 0.1 to 7 and >7 drinks/week for each types of alcoholic beverage (beer, wine and spirits), while Slagter et al. [218] classified beverage-specific consumption if that beverage type accounted for >70% of their alcohol consumption. One difficulty is how to account for the fact that people likely drink several different types of alcoholic beverages and how to quantify these overall patterns of alcohol consumption. Combining individual alcohol types into overall patterns of consumption, therefore, could provide novel insights into these associations; however, these analyses were beyond the scope of the present study.

We had substantial loss to follow-up since childhood, which might affect the generalisability of our findings to other populations. However, a comparison of the CDAH sample (n=2,200) with population data for Australian adults aged 25–34 years old showed that the proportion of participants who were current drinkers was very similar to that in the general population (86% vs 83%) [47]. The proportion who drank two drinks or more per day (the 'heavy drinkers') was similar to previous findings on high-risk alcohol consumption in young adults (11% vs 13%) [219]. Furthermore, sensitivity analysis showed small differences after applying the IPW from the adulthood and childhood data to deal with loss to follow-up (Appendix Table 3-14 to Table 3-21). Thus, the loss to follow-up does not appear to have had a great effect on our results. Despite the large sample size, we still had inadequate power to examine the types of alcohol consumed in detail. There were not enough participants consuming >20 g/day for each type of beverage to allow us to examine specific alcohol types and each individual risk factor in detail. The 'very heavy alcohol consumption' group covers a wide range of drinking, with the average consumption in this group being more than 50 g/day (>5 drinks/day). However, it is difficult from this data to determine where risk truly increased.

3.5. Conclusions

Moderate alcohol consumption was associated with a lower prevalence of MetS and some of its components even when light drinkers instead of non-drinkers were used as the reference group and account for a range of confounding factors. Although alcohol consumption plays an important role in social and culture life, health promotion messages must convey both its positive and negative effects on the cardio-metabolic health of young people.

3.6. Appendix 3.A. Additional Methods

Clinic measurements

Venous blood samples were collected from the antecubital vein after an overnight fast. Serum triglycerides, total cholesterol (mmol/L) were determined according to the Lipid Clinics Program, and high-density lipoprotein (HDL) cholesterol (mmol/L) were analysed following precipitation of apolipoprotein-B containing lipoprotein with heparin-manganese, using an Olympus AU5400 automated analyser (Olympus Optical, Tokyo, Japan). Two methods were used to determine fasting insulin (μIU/L) concentrations: a microparticle enzyme immunoassay kit (AxSYM; Abbot Laboratories, Abbot Park, IL) and an electrochemiluminescence immunoassay (Elecsys Modular Analytic E170; Roche Diagnosis, Mannheim, Switzerland). A correction factor of 0.81 was applied to the insulin values assessed with the microparticle-enzyme immunoassay. Blood pressure (BP) was measured 3 times with an automatic BP monitor after rest (Omron HEM907; Omron Health Care Inc, Kyoto, Japan). The mean of three readings was used.

Covariates

The following covariates were considered: age, sex, socio-economic (SES) quartile base on area of residence (high, medium high, medium low, or low), region, education level (university, vocational, or secondary school only), occupation (professional/manager, white collar, blue collar, or not in labour force), marital status (married or living as married versus other), and smoking status (never, former, or current), collected from questionnaires. A total physical activity score (minutes per week) was calculated from the duration, intensity, and frequency of physical activity in the past week by the International Physical Activity Questionnaire (IPAQ) [181]. Cardiorespiratory fitness (CRF) was estimated as physical work capacity (PWC) at a heart rate of 170 bpm (PWC170) on a bicycle ergometer pedalled at 60 rpm [182]. CRF was then adjusted for lean body mass to create an index uncorrelated with lean body mass because of the relation between absolute workload achieved and muscle mass [220]. Dietary intakes were assessed using a food frequency questionnaire (FFQ) assessing usual frequency of intake of food excluding alcohol intake beverages over the last 12 months, and then calculated as a Dietary Guideline Index (DGI) score, based on recommendations in the 2003 Dietary Guidelines for Australian Adults [221] and the Australian Guide to Healthy

Eating [222]. Other covariates included childhood alcohol consumption experimentation (non-drinkers or drinkers at childhood), health-related quality of life (HRQoL) (SF-12 physical and mental component scores), and depression and anxiety from the aforementioned CIDI [205].

Data analysis

Multiple imputation (MI) using chained equations with 30 estimations was used to replace missing data on covariates. The variables used in the imputations were sex, age, smoking status, education, BMI, state of residence, marital status, self-rated health from a previous adult follow-up in 2001-04 and scholastic ability from 1985.

Inverse probability weighting (IPW) was used to examine the effect of loss to follow-up. Weights were based on the inverse of the probability of providing follow-up data given variables from the previous adult follow-up (sex, age, education, self-rated health, smoking, and BMI) or, in a separate analysis, variables from 1985 (age, sex, BMI, state of residence and three measures of cardiorespiratory fitness). Unweighted and weighted models, which did not have missing covariates imputed, were then compared.

3.7. Appendix 3.B. Additional Tables and Figures

Table 3-3. Multivariable regression analyses of the association between alcohol consumption and waist circumference

Outcome: Waist circumference		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Alcohol per day	0g	1.73 (0.13, 3.33)	<0.05	2.15 (0.73, 3.56)	<0.01	1.86 (0.40, 3.32)	<0.05	1.81 (0.35, 3.27)	<0.05	1.88 (0.41, 3.36)	<0.05
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10-20g	0.81 (-0.50, 2.11)	0.224	-0.86 (-2.02, 0.29)	0.144	-1.04 (-2.24, 0.16)	0.088	-0.84 (-2.04, 0.36)	0.169	-0.79 (-2.00, 0.42)	0.200
	>20-30g	0.71 (-1.66, 3.07)	0.557	-1.01 (-3.09, 1.08)	0.344	-0.98 (-3.08, 1.12)	0.360	-0.68 (-2.78, 1.42)	0.526	-0.63 (-2.76, 1.49)	0.558
	>30g	2.88 (0.58, 5.17)	<0.05	-0.55 (-2.57, 1.47)	0.593	-0.86 (-2.91, 1.19)	0.409	-0.77 (-2.81, 1.27)	0.459	-0.80 (-2.89, 1.29)	0.454
Beer	0g	-2.84 (-3.92, -1.76)	<0.001	1.63 (0.58, 2.69)	<0.05	1.63 (0.55, 2.71)	<0.01	1.45 (0.37, 2.54)	<0.01	1.46 (0.36, 2.55)	<0.01

Outcome: Waist circumference		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	3.52 (1.77, 5.27)	<0.001	0.56 (-1.01, 2.13)	0.483	0.31 (-1.28, 1.91)	0.701	0.60 (-1.00, 2.19)	0.463	0.51 (-1.12, 2.13)	0.540
Wine	0g	3.37 (2.23, 4.50)	<0.001	1.34 (0.30, 2.37)	<0.05	1.00 (-0.08, 2.07)	0.068	0.92 (-0.16, 1.99)	0.094	1.11 (0.02, 2.20)	<0.05
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	-2.39 (-4.09, .0.70)	<0.01	-1.30 (-2.79, 0.20)	0.090	-1.31 (-2.84, 0.21)	0.091	-1.19 (-2.70, 0.33)	0.124	-1.19 (-2.72, 0.34)	0.127
Sprits	0g	-0.39 (-1.45, 0.67)	0.472	-0.16 (-1.10, 0.77)	0.731	-0.13 (-1.09, 0.83)	0.790	-0.13 (-1.09, 0.84)	0.797	-0.12 (-1.10, 0.85)	0.804
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	4.74 (1.46, 8.02)	<0.01	2.14 (-0.76, 5.03)	0.148	2.06 (-0.94, 5.07)	0.178	1.62 (-1.37, 4.61)	0.288	1.94 (-1.10, 4.98)	0.211

β = regression coefficient; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.

Table 3-4. Multivariable regression analyses of the association between alcohol consumption and triglycerides

Outcome:		**Unadjusted**		**Adjusted**							
Triglycerides				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Alcohol per day	0g	0.02 (-0.08, 0.12)	0.739	0.03 (-0.07, 0.13)	0.517	0.03 (-0.07, 0.12)	0.619	0.01 (-0.09, 0.11)	0.814	-0.01 (-0.11, 0.10)	0.897
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10-20g	0.09 (0.01, 0.17)	<0.05	0.03 (-0.06, 0.11)	0.506	-0.01 (-0.09, 0.07)	0.800	-0.01 (-0.09, 0.08)	0.882	-0.01 (-0.10, 0.08)	0.840
	>20-30g	0.01 (-0.15, 0.16)	0.940	-0.05 (-0.20, 0.10)	0.527	-0.08 (-0.23, 0.07)	0.286	-0.08 (-0.23, 0.07)	0.284	-0.10 (-0.24, 0.06)	0.246
	>30g	0.11 (-0.04, 0.26)	0.140	0.02 (-0.13, 0.17)	0.781	-0.01 (-0.15, 0.14)	0.964	0.01 (-0.14, 0.15)	0.970	-0.02 (-0.17, 0.13)	0.812
Beer	0g	-0.05 (-0.12, 0.02)	0.142	0.07 (-0.01, 0.15)	0.057	0.08 (0.01, 0.15)	<0.05	0.07 (-0.01, 0.14)	0.079	0.07 (-0.01, 0.14)	0.094
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.14 (0.02, 0.25)	<0.05	0.03 (-0.08, 0.15)	0.604	0.02 (-0.10, 0.13)	0.779	0.02 (-0.10, 0.13)	0.776	-0.01 (-0.12, 0.11)	0.957

Outcome:		**Unadjusted**		**Adjusted**							
Triglycerides				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Wine	0g	0.10 (0.03, 0.18)	<0.01	0.06 (-0.02, 0.14)	0.117	0.05 (-0.02, 0.12)	0.185	0.04 (-0.03, 0.11)	0.284	0.04 (-0.04, 0.12)	0.288
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.01 (-0.11, 0.11)	0.959	0.03 (-0.08, 0.13)	0.647	-0.02 (-0.13, 0.08)	0.667	-0.01 (-0.12, 0.09)	0.785	-0.01 (-0.12, 0.10)	0.879
Sprits	0g	-0.06 (-0.13, 0.01)	0.082	-0.05 (-0.12, 0.02)	0.169	-0.05 (-0.12, 0.02)	0.109	-0.06 (-0.13, 0.01)	0.075	-0.06 (-0.13, 0.01)	0.072
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.24 (0.03, 0.46)	<0.05	0.20 (-0.02, 0.41)	0.069	0.16 (-0.05, 0.37)	0.136	0.14 (-0.07, 0.34)	0.203	0.12 (-0.10, 0.34)	0.290

β = regression coefficient; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.

Table 3-5. Multivariable regression analyses of the association between alcohol consumption and HDL cholesterol

Outcome:		**Unadjusted**		**Adjusted**							
HDL cholesterol				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Alcohol per day	0g	-0.04 (-0.08, -0.01)	<0.05	-0.06 (-0.10, -0.03)	<0.01	-0.06 (-0.10, -0.02)	<0.01	-0.06 (-0.10, -0.02)	<0.01	-0.06 (-0.10, -0.01)	<0.01
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10-20g	0.04 (0.01, 0.08)	<0.05	0.09 (0.06, 0.12)	<0.001	0.10 (0.06, 0.13)	<0.001	0.09 (0.06, 0.12)	<0.001	0.09 (0.06, 0.13)	<0.001
	>20-30g	0.13 (0.07, 0.20)	<0.001	0.19 (0.14, 0.25)	<0.001	0.20 (0.14, 0.26)	<0.001	0.20 (0.14, 0.26)	<0.001	0.20 (0.14, 0.26)	<0.001
	>30g	0.12 (0.06, 0.18)	<0.001	0.21 (0.15, 0.26)	<0.001	0.21 (0.16, 0.27)	<0.001	0.21 (0.15, 0.27)	<0.001	0.22 (0.16, 0.28)	<0.001
Beer	0g	0.04 (0.01, 0.07)	<0.01	-0.09 (-0.12, -0.06)	<0.001	-0.09 (-0.12, -0.06)	<0.001	-0.09 (-0.12, -0.06)	<0.001	-0.08 (-0.11, -0.05)	<0.001
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.07 (0.02, 0.12)	<0.01	0.15 (0.11, 0.19)	<0.001	0.15 (0.11, 0.20)	<0.001	0.15 (0.11, 0.20)	<0.001	0.16 (0.11, 0.20)	<0.001

Outcome:		**Unadjusted**		**Adjusted**							
HDL cholesterol				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Wine	0g	-0.10 (-0.13, -0.07)	<0.001	-0.07 (-0.10, -0.04)	<0.001	-0.06 (-0.09, -0.03)	<0.001	-0.06 (-0.09, -0.03)	<0.001	-0.06 (-0.09, -0.03)	<0.001
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.14 (0.10, 0.19)	<0.001	0.12 (0.08, 0.16)	<0.001	0.12 (0.08, 0.17)	<0.001	0.12 (0.08, 0.16)	<0.001	0.13 (0.09, 0.17)	<0.001
Sprits	0g	0.01 (-0.03, 0.03)	0.987	-0.01 (-0.04, 0.01)	0.367	-0.01 (-0.04, 0.01)	0.334	-0.01 (-0.04, 0.01)	0.302	-0.01 (-0.04, 0.01)	0.305
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.04 (-0.05, 0.13)	0.358	0.10 (0.02, 0.19)	<0.05	0.11 (0.03, 0.20)	<0.01	0.12 (0.04, 0.21)	<0.01	0.13 (0.04, 0.22)	<0.01

β = regression coefficient; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.

Table 3-6. Multivariable regression analyses of the association between alcohol consumption and systolic blood pressure

Outcome: Systolic blood pressure		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Alcohol per day	0g	-1.02 (-2.59, 0.56)	0.207	0.40 (-0.96, 1.76)	0.567	-0.03 (-1.46, 1.41)	0.973	-0.06 (-1.51, 1.38)	0.932	-0.14 (-1.60, 1.33)	0.856
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10-20g	2.52 (1.20, 3.83)	<0.001	0.11 (-1.04, 1.25)	0.857	0.05 (-1.14, 1.23)	0.934	0.09 (-1.10, 1.29)	0.879	0.14 (-1.07, 1.36)	0.817
	>20-30g	3.55 (1.14, 5.97)	<0.01	0.79 (-1.28, 2.86)	0.455	0.93 (-1.17, 3.02)	0.385	0.88 (-1.23, 2.99)	0.411	1.02 (-1.12, 3.16)	0.351
	>30g	6.52 (4.19, 8.85)	<0.001	2.91 (0.91, 4.91)	<0.01	3.04 (0.99, 5.08)	<0.01	3.13 (1.08, 5.18)	<0.01	3.01 (0.90, 5.12)	<0.01
Beer	0g	-5.80 (-6.87, -4.74)	<0.001	-0.12 (-1.15, 0.92)	0.826	-0.22 (-1.29, 0.85)	0.691	-0.28 (-1.36, 0.80)	0.609	-0.45 (-1.55, 0.64)	0.417
	>0-10g	Reference		Reference		Reference		Reference		Reference	

Outcome: Systolic blood pressure		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>10g	4.26 (2.51, 6.02)	<0.001	0.86 (-0.69, 2.42)	0.276	0.83 (-0.76, 2.42)	0.306	0.87 (-0.73, 2.47)	0.286	0.72 (-0.92, 2.35)	0.390
Wine	0g	2.34 (1.18, 3.50)	<0.001	0.69 (-0.32, 1.70)	0.180	0.48 (-0.58, 1.54)	0.375	0.49 (-0.58, 1.56)	0.368	0.51 (-0.58, 1.60)	0.359
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.88 (-0.87, 2.62)	0.325	2.32 (0.84, 3.79)	<0.01	2.36 (0.84, 3.87)	<0.01	2.42 (0.90, 3.93)	<0.01	2.40 (0.87, 3.94)	<0.01
Sprits	0g	-0.72 (-1.79, 0.35)	0.187	0.22 (-0.70, 1.13)	0.643	0.07 (-0.88, 1.02)	0.881	0.19 (-0.77, 1.15)	0.695	0.35 (-0.63, 1.32)	0.486
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	3.20 (-0.21, 6.62)	0.066	0.08 (-2.82, 2.90)	0.955	-0.01 (-3.04, 3.01)	0.994	-0.07 (-3.09, 2.96)	0.966	0.34 (-2.75, 3.43)	0.828

β = regression coefficient; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.

Table 3-7. Multivariable regression analyses of the association between alcohol consumption and diastolic blood pressure

Outcome: Diastolic blood pressure		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Alcohol per day	0g	0.61 (-0.54, 1.76)	0.300	1.02 (-0.11, 2.15)	0.078	0.78 (-0.41, 1.97)	0.198	0.68 (-0.51, 1.88)	0.263	0.75 (-0.46, 1.96)	0.223
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10-20g	0.55 (-0.41, 1.51)	0.258	-0.34 (-1.29, 0.61)	0.479	-0.30 (-1.29, 0.68)	0.546	-0.15 (-1.13, 0.84)	0.772	-0.14 (-1.14, 0.86)	0.782
	>20-30g	1.80 (0.04, 3.56)	<0.05	0.90 (-0.82, 2.62)	0.305	1.01 (-0.73, 2.74)	0.256	1.16 (-0.58, 2.90)	0.191	1.19 (-0.58, 2.96)	0.187
	>30g	3.85 (2.16, 5.55)	<0.001	2.56 (0.89, 4.22)	<0.01	2.28 (0.59, 3.97)	<0.01	2.37 (0.68, 4.07)	<0.01	2.07 (0.33, 3.81)	<0.05
Beer	0g	-1.55 (-2.34, -0.75)	<0.001	0.39 (-0.46, 1.25)	0.369	0.35 (-0.53, 1.24)	0.435	0.20 (-0.69, 1.09)	0.657	0.07 (-0.83, 0.97)	0.880
	>0-10g	Reference		Reference		Reference		Reference		Reference	

Outcome: Diastolic blood pressure		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>10g	2.01 (0.70, 3.32)	<0.01	0.82 (-0.47, 2.11)	0.212	0.81 (-0.50, 2.13)	0.226	0.93 (-0.40, 2.25)	0.170	0.68 (-0.67, 2.02)	0.327
Wine	0g	1.38 (0.54, 2.21)	<0.01	0.74 (-0.10, 1.58)	0.084	0.65 (-0.23, 1.53)	0.148	0.59 (-0.30, 1.47)	0.193	0.75 (-0.14, 1.65)	0.100
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	1.08 (-0.18, 2.34)	0.094	1.56 (0.33, 2.79)	<0.05	1.57 (0.32, 2.83)	<0.05	1.68 (0.43, 2.94)	<0.01	1.65 (0.39, 2.92)	<0.05
Sprits	0g	-0.30 (-1.07, 0.48)	0.454	-0.06 (-0.82, 0.70)	0.881	-0.07 (-0.86, 0.73)	0.871	-0.03 (-0.82, 0.77)	0.948	0.06 (-0.75, 0.86)	0.891
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	1.54 (-0.93, 4.01)	0.222	0.40 (-2.02, 2.82)	0.747	0.06 (-2.45, 2.57)	0.965	-0.22 (-2.72, 2.29)	0.865	0.17 (-2.38, 2.72)	0.896

β = regression coefficient; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.

Table 3-8. Multivariable regression analyses of the association between alcohol consumption and glucose

Outcome: Glucose		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Alcohol per day	0g	-0.03 (-0.09, 0.03)	0.305	0.01 (-0.05, 0.06)	0.963	-0.01 (-0.06, 0.05)	0.932	-0.01 (-0.06, 0.06)	0.975	-0.01 (-0.06, 0.05)	0.911
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10-20g	0.05 (0.01, 0.10)	<0.05	-0.02 (-0.06, 0.03)	0.515	-0.01 (-0.06, 0.04)	0.677	-0.01 (-0.05, 0.04)	0.869	0.01 (-0.05, 0.05)	0.966
	>20-30g	0.10 (0.01, 0.19)	<0.05	0.03 (-0.05, 0.12)	0.413	0.03 (-0.05, 0.11)	0.468	0.04 (-0.05, 0.12)	0.396	0.03 (-0.05, 0.12)	0.458
	>30g	0.15 (0.06, 0.23)	<0.01	0.05 (-0.03, 0.13)	0.209	0.04 (-0.04, 0.12)	0.380	0.03 (-0.05, 0.12)	0.394	0.04 (-0.04, 0.12)	0.346
Beer	0g	-0.14 (-0.18, -0.10)	<0.001	0.01 (-0.04, 0.04)	0.902	0.01 (-0.04, 0.04)	0.935	-0.01 (-0.05, 0.04)	0.866	0.01 (-0.04, 0.05)	0.828
	>0-10g	Reference		Reference		Reference		Reference		Reference	

Outcome:		**Unadjusted**		**Adjusted**							
Glucose											
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>10g	0.14 (0.07, 0.21)	<0.001	0.06 (-0.01, 0.13)	0.051	0.05 (-0.02, 0.11)	0.147	0.04 (-0.02, 0.11)	0.177	0.05 (-0.02, 0.11)	0.173
Wine	0g	0.05 (0.01, 0.09)	<0.05	0.01 (-0.03, 0.05)	0.602	0.01 (-0.04, 0.05)	0.782	0.01 (-0.04, 0.05)	0.794	0.01 (-0.04, 0.05)	0.781
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.04 (-0.03, 0.10)	0.269	0.04 (-0.01, 0.10)	0.142	0.03 (-0.03, 0.09)	0.296	0.03 (-0.02, 0.09)	0.249	0.04 (-0.02, 0.10)	0.199
Sprits	0g	-0.03 (-0.07, 0.01)	0.139	-0.02 (-0.06, 0.02)	0.252	-0.02 (-0.06, 0.02)	0.293	-0.02 (-0.05, 0.02)	0.352	-0.02 (-0.05, 0.02)	0.437
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.01 (-0.12, 0.13)	0.942	-0.03 (-0.15, 0.09)	0.654	-0.02 (-0.14, 0.09)	0.712	-0.03 (-0.14, 0.09)	0.663	-0.03 (-0.16, 0.09)	0.582
	p-trend	*0.232*		*0.222*		*0.194*		*0.223*		*0.214*	

β = regression coefficient; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.

Table 3-9. Multivariable regression analyses of the association between alcohol consumption and prevalence of metabolic syndrome

Outcome: Prevalence MetS		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		PR (95% CI)	P_{value}	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
Alcohol per day	0g	1.16 (0.75, 1.80)	0.493	1.26 (0.82, 1.95)	0.289	1.36 (0.86, 2.16)	0.183	1.40 (0.89, 2.20)	0.142	1.41 (0.90, 2.21)	0.137
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10-20g	0.76 (0.49, 1.16)	0.202	0.66 (0.43, 1.02)	0.064	0.63 (0.41, 0.97)	<0.05	0.63 (0.41, 0.98)	<0.05	0.64 (0.41, 0.99)	<0.05
	>20-30g	0.49 (0.18, 1.31)	0.154	0.45 (0.17, 1.21)	0.116	0.44 (0.16, 1.19)	0.106	0.46 (0.17, 1.23)	0.123	0.45 (0.17, 1.21)	0.114
	>30g	1.04 (0.54, 2.02)	0.896	0.69 (0.36, 1.33)	0.263	0.69 (0.35, 1.38)	0.295	0.70 (0.35, 1.41)	0.320	0.72 (0.36, 1.43)	0.343
Beer	0g	0.98 (0.70, 1.35)	0.847	1.53 (1.07, 2.18)	<0.05	1.62 (1.13, 2.32)	<0.01	1.63 (1.14, 2.32)	<0.01	1.62 (1.14, 2.32)	<0.01
	>0-10g	Reference		Reference		Reference		Reference		Reference	

Outcome: Prevalence MetS		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		PR (95% CI)	P_{value}	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
	>10g	1.06 (0.63, 1.78)	0.741	0.83 (0.49, 1.40)	0.487	0.79 (0.46, 1.36)	0.391	0.84 (0.49, 1.45)	0.534	0.85 (0.49, 1.46)	0.546
Wine	0g	2.01 (1.46, 2.79)	<0.001	1.57 (1.13, 2.19)	<0.01	1.56 (1.10, 2.21)	<0.05	1.60 (1.13, 2.27)	<0.01	1.59 (1.12, 2.25)	<0.01
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	1.08 (0.60, 1.92)	0.807	1.15 (0.65, 2.03)	0.643	1.17 (0.66, 2.08)	0.596	1.20 (0.67, 2.13)	0.544	1.21 (0.68, 2.14)	0.524
Sprits	0g	0.95 (0.69, 1.31)	0.764	1.01 (0.73, 1.38)	0.973	1.05 (0.75, 1.46)	0.784	1.05 (0.75, 1.46)	0.773	1.06 (0.76, 1.47)	0.748
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	1.32 (0.56, 3.13)	0.524	0.87 (0.37, 2.04)	0.747	0.90 (0.37, 2.20)	0.816	0.83 (0.34, 2.02)	0.679	0.84 (0.34, 2.04)	0.699

PR = prevalence ratio; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.

Table 3-10. Multivariable regression analyses of the association between alcohol consumption and continuous metabolic syndrome risk score

Outcome: Continuous MetS risk score		**Unadjusted**		**Adjusted**							
				Model 1		Model 2		Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Alcohol per day	0g	0.13 (0.03, 0.22)	<0.01	0.09 (-0.01, 0.19)	0.059	0.09 (-0.01, 0.19)	0.068	0.08 (-0.02, 0.18)	0.093	0.08 (-0.03, 0.17)	0.130
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10-20g	-0.12 (-0.20, -0.04)	<0.01	-0.10 (-0.18, -0.03)	<0.01	-0.10 (-0.18, -0.02)	<0.05	-0.09 (-0.17, -0.01)	<0.05	-0.09 (-0.17, -0.01)	<0.05
	>20-30g	-0.17 (-0.31, -0.04)	<0.05	-0.14 (-0.27, 0.01)	0.052	-0.14 (-0.28, -0.01)	<0.05	-0.13 (-0.26, 0.01)	0.073	-0.13 (-0.27, 0.01)	0.069
	>30g	-0.04 (-0.18, 0.09)	0.532	-0.06 (-0.19, 0.07)	0.386	-0.07 (-0.21, 0.06)	0.304	-0.06 (-0.20, 0.07)	0.353	-0.08 (-0.21, 0.06)	0.277
Beer	0g	0.13 (0.07, 0.20)	<0.001	0.13 (0.06, 0.20)	<0.001	0.13 (0.06, 0.20)	<0.001	0.11 (0.04, 0.19)	<0.01	0.11 (0.04, 0.18)	<0.01
	>0-10g	Reference		Reference		Reference		Reference		Reference	

Outcome: Continuous MetS risk score		**Unadjusted**		Model 1		Model 2		**Adjusted** Model 3		Model 4	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>10g	-0.01 (-0.10, 0.10)	0.996	-0.02 (-0.13, 0.08)	0.690	-0.03 (-0.14, 0.07)	0.570	-0.02 (-0.13, 0.08)	0.687	-0.03 (-0.14, 0.07)	0.526
Wine	0g	0.14 (0.08, 0.21)	<0.001	0.10 (0.03, 0.17)	<0.01	0.09 (0.02, 0.16)	<0.01	0.09 (0.01, 0.16)	<0.05	0.09 (0.02, 0.16)	<0.05
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	-0.06 (-0.16, 0.04)	0.248	-0.05 (-0.15, 0.05)	0.301	-0.06 (-0.16, 0.04)	0.259	-0.05 (-0.15, 0.05)	0.362	-0.05 (-0.15, 0.05)	0.303
Sprits	0g	-0.01 (-0.07, 0.05)	0.754	-0.02 (-0.08, 0.04)	0.495	-0.02 (-0.08, 0.05)	0.567	-0.02 (-0.08, 0.05)	0.592	-0.02 (-0.08, 0.05)	0.557
	>0-10g	Reference		Reference		Reference		Reference		Reference	
	>10g	0.01 (-0.19, 0.20)	0.953	-0.01 (-0.21, 0.19)	0.900	-0.02 (-0.22, 0.18)	0.834	-0.05 (-0.25, 0.15)	0.615	-0.06 (-0.26, 0.15)	0.586

β = regression coefficient; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.

Table 3-11. Multivariable regression analyses of the association between alcohol consumption measured in a continuous term (per standard drink per day) and each component of metabolic syndrome and continuous metabolic syndrome risk score

Outcome	**Unadjusted**		**Adjusted**							
			Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Waist circumference										
Total (1 drink/day)	0.42 (0.05, 0.80)	<0.05	-0.28 (-0.61, 0.05)	0.101	-0.28 (-0.62, 0.06)	0.108	-0.24 (-0.58, 0.10)	0.168	-0.24 (-0.57, 0.11)	0.189
Beer (1 drink/day)	1.72 (1.19, 2.25)	<0.001	-0.07 (-0.56, 0.42)	0.788	-0.09 (-0.59, 0.41)	0.716	-0.05 (-0.55, 0.45)	0.840	-0.01 (-0.52, 0.51)	0.980
Wine (1 drink/day)	-1.73 (-2.39, -1.07)	<0.001	-0.85 (-1.44, -0.26)	<0.01	-0.78 (-1.37, -0.19)	<0.05	-0.70 (-1.29, -0.11)	<0.05	-0.75 (-1.34, -0.16)	<0.05
Spirit (1 drink/day)	2.27 (0.67, 3.88)	<0.01	0.46 (-0.97, 1.90)	0.529	0.40 (-1.08, 1.88)	0.592	0.32 (-1.15, 1.79)	0.666	0.47 (-1.02, 1.95)	0.538
Triglycerides										
Total (1 drink/day)	0.03 (0.01, 0.06)	<0.05	0.01 (-0.01, 0.04)	0.310	0.01 (-0.02, 0.03)	0.583	0.01 (-0.02, 0.03)	0.476	0.01 (-0.02. 0.03)	0.672

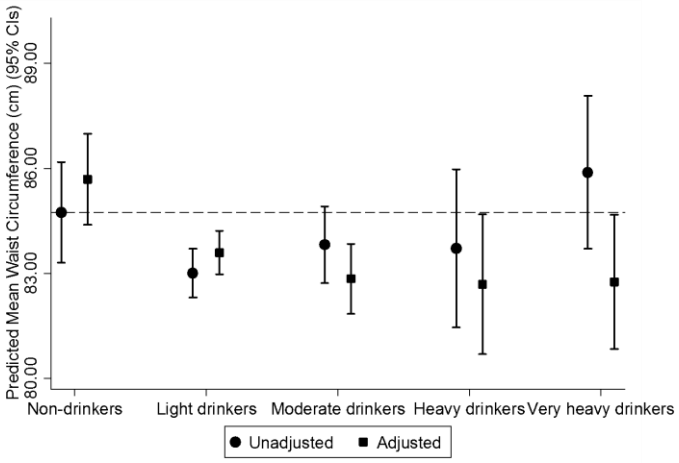
Outcome	**Unadjusted**		**Adjusted**							
			Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Beer (1 drink/day)	0.07 (0.03, 0.10)	<0.001	0.02 (-0.02, 0.06)	0.284	0.02 (-0.02, 0.05)	0.322	0.02 (-0.02, 0.05)	0.293	0.01 (-0.03, 0.05)	0.638
Wine (1 drink/day)	-0.02 (-0.07, 0.02)	0.298	-0.01 (-0.05, 0.04)	0.877	-0.02 (-0.06, 0.03)	0.441	-0.01 (-0.05, 0.03)	0.579	-0.01 (-0.05, 0.03)	0.698
Spirit (1 drink/day)	0.12 (0.02, 0.21)	<0.05	0.08 (-0.02, 0.17)	0.118	0.06 (-0.03, 0.16)	0.198	0.06 (-0.03, 0.16)	0.198	0.08 (-0.03, 0.19)	0.149
HDL-cholesterol										
Total (1 drink/day)	0.03 (0.02, 0.04)	<0.001	0.05 (0.04, 0.06)	<0.001	0.05 (0.04, 0.06)	<0.001	0.05 (0.04, 0.06)	<0.001	0.05 (0.04, 0.06)	<0.001
Beer (1 drink/day)	0.01 (-0.01, 0.02)	0.753	0.05 (0.04, 0.06)	<0.001	0.05 (0.04, 0.06)	<0.001	0.05 (0.04, 0.06)	<0.001	0.05 (0.04, 0.07)	<0.001
Wine (1 drink/day)	0.09 (0.07, 0.11)	<0.001	0.07 (0.06, 0.09)	<0.001	0.07 (0.06, 0.09)	<0.001	0.07 (0.05, 0.09)	<0.001	0.07 (0.05, 0.09)	<0.001
Spirit (1 drink/day)	0.03 (-0.01, 0.07)	0.148	0.07 (0.03, 0.11)	<0.001	0.08 (0.04, 0.11)	<0.001	0.08 (0.04, 0.12)	<0.001	0.09 (0.05, 0.13)	<0.001

Outcome	**Unadjusted**		**Adjusted**							
			Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Systolic blood pressure										
Total (1 drink/day)	1.35 (0.97, 1.72)	<0.001	0.42 (0.10, 0.75)	<0.05	0.48 (0.15, 0.82)	<0.01	0.49 (0.16, 0.83)	<0.01	0.49 (0.15, 0.84)	<0.01
Beer (1 drink/day)	2.74 (2.21, 3.27)	<0.001	0.55 (0.07, 1.03)	<0.05	0.62 (0.12, 1.11)	<0.05	0.64 (0.14, 1.13)	<0.05	0.66 (0.15, 1.18)	<0.05
Wine (1 drink/day)	-0.24 (-0.92, 0.44)	0.482	0.68 (0.10, 1.26)	<0.05	0.73 (0.14, 1.31)	<0.05	0.74 (0.15, 1.33)	<0.05	0.70 (0.11, 1.30)	<0.05
Spirit (1 drink/day)	1.60 (-0.05, 3.26)	0.057	-0.88 (-2.31, 0.55)	0.226	-0.81 (-2.28, 0.67)	0.283	-0.82 (-2.30, 0.65)	0.274	-0.83 (-2.33, 0.67)	0.278
Diastolic blood pressure										
Total (1 drink/day)	0.67 (0.39, 0.94)	<0.001	0.36 (0.09, 0.63)	<0.01	0.36 (0.08, 0.64)	<0.05	0.39 (0.11, 0.66)	<0.01	0.36 (0.07, 0.64)	<0.05
Beer (1 drink/day)	1.30 (0.91, 1.69)	<0.001	0.60 (0.20, 1.00)	<0.01	0.59 (0.18, 1.01)	<0.01	0.62 (0.21, 1.04)	<0.01	0.61 (0.18, 1.03)	<0.01

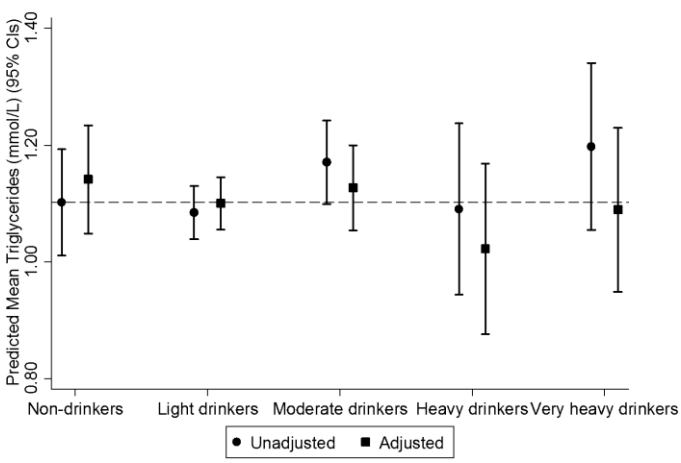
Outcome	**Unadjusted**		**Adjusted**							
			Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Wine (1 drink/day)	-0.02 (-0.51, 0.47)	0.935	0.29 (-0.19, 0.77)	0.233	0.29 (-0.20, 0.78)	0.244	0.34 (-0.14, 0.83)	0.166	0.28 (-0.21, 0.77)	0.262
Spirit (1 drink/day)	0.67 (-0.52, 1.87)	0.270	-0.14 (-1.33, 1.05)	0.814	-0.14 (-1.36, 1.09)	0.826	-0.17 (-1.39, 1.05)	0.788	-0.17 (-1.41, 1.06)	0.783
Glucose										
Total (1 drink/day)	0.03 (0.02, 0.04)	<0.001	0.01 (-0.01, 0.02)	0.422	0.01 (-0.01, 0.02)	0.457	0.01 (-0.01, 0.02)	0.437	0.01 (-0.01, 0.02)	0.455
Beer (1 drink/day)	0.07 (0.05, 0.09)	<0.001	0.01 (-0.01, 0.03)	0.215	0.01 (-0.01, 0.03)	0.176	0.01 (-0.01, 0.03)	0.193	0.01 (-0.01, 0.03)	0.260
Wine (1 drink/day)	-0.01 (-0.03, 0.02)	0.484	0.01 (-0.02, 0.03)	0.681	0.01 (-0.02, 0.03)	0.781	0.01 (-0.02, 0.03)	0.682	0.01 (-0.02, 0.03)	0.701
Spirit (1 drink/day)	0.01 (-0.05, 0.06)	0.962	-0.03 (-0.08, 0.03)	0.302	-0.03 (-0.09, 0.02)	0.192	-0.04 (-0.09, 0.02)	0.188	-0.03 (-0.09, 0.03)	0.317
Continuous MetS risk score										

Outcome	**Unadjusted**		**Adjusted**					
			Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}	β (95% CI)	P_{value}
Total (1 drink/day)	-0.03 (-0.05, -0.01)	<0.05	-0.02 (-0.04, 0.01)	0.052	-0.02 (-0.05, -0.01)	<0.05	-0.02 (-0.04, 0.01)	0.079	-0.02 (-0.04, 0.01)	0.059
Beer (1 drink/day)	-0.01 (-0.04, 0.02)	0.642	-0.01 (-0.04, 0.03)	0.700	-0.01 (-0.04, 0.03)	0.699	-0.01 (-0.04, 0.03)	0.805	-0.01 (-0.04, 0.03)	0.760
Wine (1 drink/day)	-0.06 (-0.10, -0.02)	<0.01	-0.05 (-0.09, -0.01)	<0.01	-0.05 (-0.09, -0.01)	<0.01	-0.05 (-0.08, -0.01)	<0.05	-0.05 (-0.09, -0.01)	<0.05
Spirit (1 drink/day)	-0.04 (-0.13, 0.06)	0.450	-0.04 (-0.14, 0.05)	0.379	-0.05 (-0.15, 0.05)	0.292	-0.06 (-0.15, 0.04)	0.257	-0.06 (-0.16, 0.04)	0.253

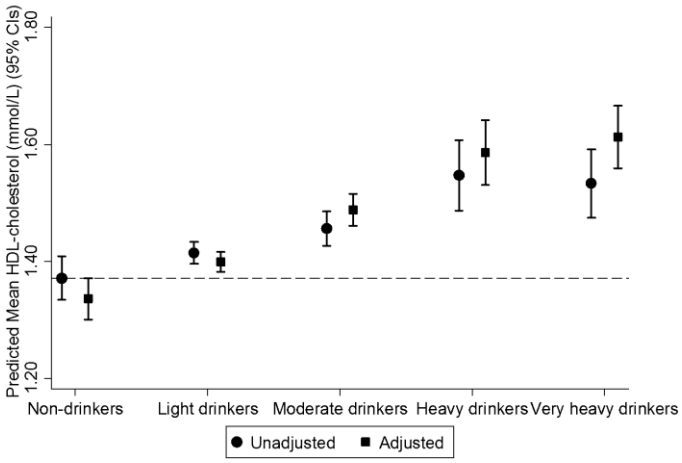
β = regression coefficient; CI=confidence interval. Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, dietary intakes, physical activity. Model 3 adjusted for Model 2 + cardiorespiratory fitness. Model 4 adjusted for Model 3 + depression and anxiety.



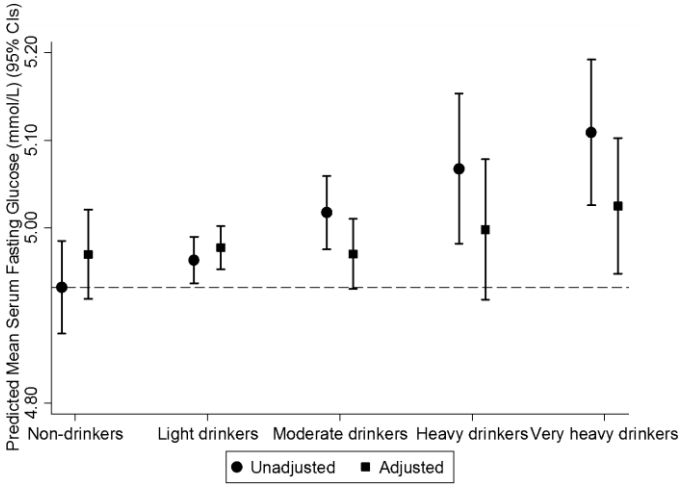
Waist circumference (A)



Serum Triglycerides (B)



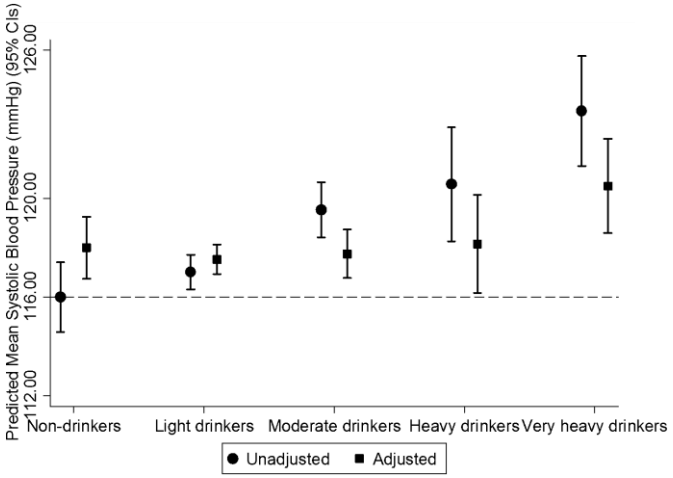
Serum HDL-cholesterol (C)



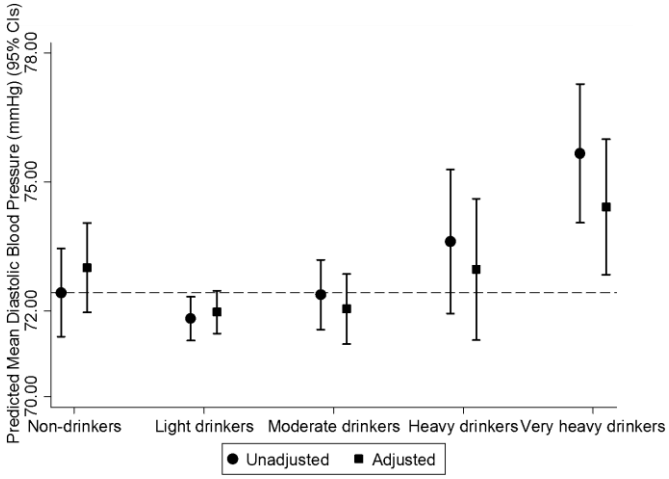
Fasting blood glucose (D)

Figure 3-4. Predicted means of waist circumference (A), triglycerides (B), HDL-cholesterol (C), and serum fasting blood glucose (D) according to alcohol consumption in multivariable regression models using non-drinker group as the reference category.

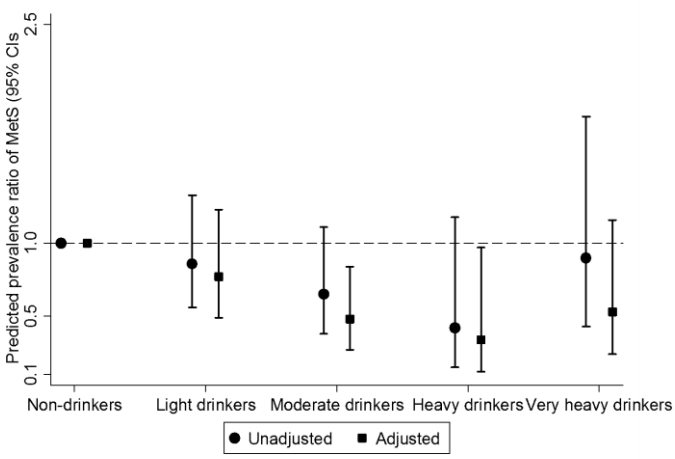
Bars represent 95% confidence intervals. Adjusted models include sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety. Details can be found in the Appendix, Table 3-22.



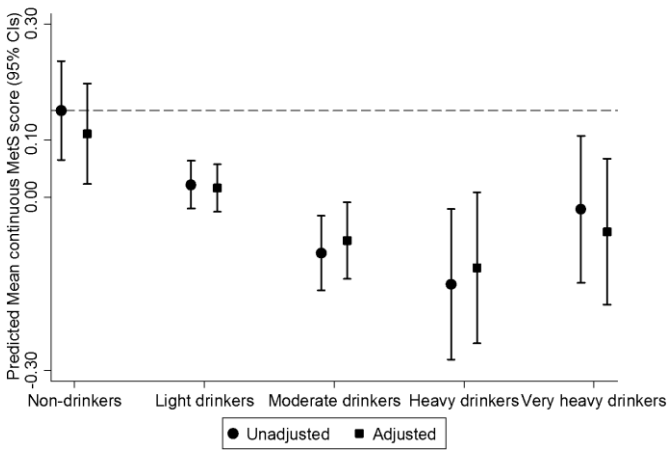
Systolic Blood Pressure (E)



Diastolic Blood Pressure (F)



Prevalence ratio of MetS (G)



Continuous MetS Risk Score (H)

Figure 3-5: Distribution of predicted means of systolic blood pressure (E) and diastolic blood pressure (F), prevalence ratio of MetS (G) and predicted mean value of continuous MetS risk score (H) according to alcohol consumption status in multivariable regression models using non-drinker group as the reference category.

Bars represent 95% confidence intervals. All models were adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical

activity, cardiorespiratory fitness and depression and anxiety. Details can be found in the Appendix, Table 3-22, Table 3-23.

Table 3-12. Sensitivity analysis of the association between alcohol consumption and continuous metabolic syndrome risk score and components of metabolic syndrome after excluding participants with alcohol dependence

Outcome	Exposure Alcohol per day	All participants		Excluding those with an alcohol dependence	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}
Continuous MetS risk score	0g	0.08 (-0.03, 0.17)	0.130	0.09 (-0.01, 0.19)	0.079
	>0-10g	Reference		Reference	
	>10-20g	-0.09 (-0.17, -0.01)	<0.05	-0.10 (-0.18, -0.01)	<0.05
	>20-30g	-0.13 (-0.27, 0.01)	0.069	-0.16 (-0.31, 0.00)	0.050
	>30g	-0.08 (-0.21, 0.06)	0.277	-0.08 (-0.25, 0.09)	0.342
Waist circumference	0g	1.88 (0.41, 3.36)	<0.05	2.08 (0.57, 3.59)	<0.001
	>0-10g	Reference		Reference	
	>10-20g	-0.79 (-2.00, 0.42)	0.200	-0.39 (-1.69, 0.90)	0.552
	>20-30g	-0.63 (-2.76, 1.49)	0.558	-0.99 (-3.36, 1.38)	0.413
	>30g	-0.80 (-2.89, 1.29)	0.454	-1.21 (-3.72, 1.31)	0.346
Triglycerides	0g	-0.01 (-0.11, 0.10)	0.897	-0.01 (-0.11, 0.10)	0.918
	>0-10g	Reference		Reference	

Outcome	Exposure Alcohol per day	All participants		Excluding those with an alcohol dependence	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>10-20g	-0.01 (-0.10, 0.08)	0.840	-0.02 (-0.12, 0.07)	0.599
	>20-30g	-0.10 (-0.24, 0.06)	0.246	-0.12 (-0.28, 0.05)	0.171
	>30g	-0.02 (-0.17, 0.13)	0.812	-0.06 (-0.24, 0.12)	0.498
HDL cholesterol	0g	-0.06 (-0.10, -0.01)	<0.01	-0.06 (-0.10, -0.01)	<0.01
	>0-10g	Reference		Reference	
	>10-20g	0.09 (0.06, 0.13)	<0.001	0.09 (0.06, 0.13)	<0.001
	>20-30g	0.20 (0.14, 0.26)	<0.001	0.18 (0.11, 0.24)	<0.001
	>30g	0.22 (0.16, 0.28)	<0.001	0.21 (0.14, 0.28)	<0.001
Systolic BP	0g	-0.14 (-1.60, 1.33)	0.856	-0.06 (-1.54, 1.41)	0.935
	>0-10g	Reference		Reference	
	>10-20g	0.14 (-1.07, 1.36)	0.817	-0.35 (-1.63, 0.93)	0.589
	>20-30g	1.02 (-1.12, 3.16)	0.351	0.46 (-1.90, 2.81)	0.704
	>30g	3.01 (0.90, 5.12)	<0.01	4.28 (1.79, 6.78)	<0.01
Diastolic BP	0g	0.75 (-0.46, 1.96)	0.223	0.88 (-0.32, 2.09)	0.151
	>0-10g	Reference		Reference	
	>10-20g	-0.14 (-1.14, 0.86)	0.782	-0.61 (-1.65, 0.44)	0.258

Outcome	Exposure Alcohol per day	All participants		Excluding those with an alcohol dependence	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>20-30g	1.19 (-0.58, 2.96)	0.187	0.66 (-1.27, 2.59)	0.504
	>30g	2.07 (0.33, 3.81)	<0.05	2.48 (0.43, 4.52)	<0.05
Glucose	0g	-0.01 (-0.06, 0.05)	0.911	0.01 (-0.06, 0.06)	0.963
	>0-10g	Reference		Reference	
	>10-20g	0.01 (-0.05, 0.05)	0.966	0.01 (-0.05, 0.06)	0.890
	>20-30g	0.03 (-0.05, 0.12)	0.458	0.01 (-0.08, 0.11)	0.834
	>30g	0.04 (-0.04, 0.12)	0.346	0.03 (-0.07, 0.13)	0.527

Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-13. Sensitivity analysis of the association between alcohol consumption and prevalence of metabolic syndrome after excluding participants with alcohol dependence

Outcome	All participants		Excluding those with an alcohol dependence	
Prevalence MetS	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
Alcohol per day				
0g	1.41 (0.90, 2.21)	0.137	1.23 (0.76, 1.99)	0.403
>0-10g	Reference		Reference	
>10-20g	0.64 (0.41, 0.99)	<0.05	0.71 (0.45, 1.14)	0.159
>20-30g	0.45 (0.17, 1.21)	0.114	0.46 (0.16, 1.37)	0.163
>30g	0.72 (0.36, 1.43)	0.343	0.89 (0.41, 1.96)	0.780

Abbreviation: MetS=metabolic syndrome; PR=prevalence ratios; CI=confidence interval.

Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-14. Sensitivity analysis of applying inverse probability weighting in analyses of the association between alcohol consumption and waist circumference

Outcomes	Multiple imputation	Inverse probability weighting		
Waist circumference		Unweighted	Weighted with adult variables*	Weighted with childhood variables†
	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)
0g	1.88 (0.41, 3.36)	2.48 (0.88, 4.09)	2.61 (0.58, 4.65)	3.22 (0.95, 5.49)
>0-10g	Reference	Reference	Reference	Reference
>10-20g	-0.79 (-2.00, 0.42)	-0.79 (-2.08, 0.50)	-1.10 (-2.41, 0.20)	-0.64 (-2.13, 0.85)
>20-30g	-0.63 (-2.76, 1.49)	-0.85 (-3.11, 1.40)	-1.12 (-3.02, 0.78)	-1.22 (-3.50, 1.07)
>30g	-0.80 (-2.89, 1.29)	-1.27 (-3.55, 1.02)	-1.19 (-3.41, 1.03)	0.33 (-1.40, 2.06)

* Adult variables for weights were from current follow-up in 2004-06 and included age, sex, education level, self-rated health, state of residence. See methods for details.

† Child variables for weights were from the 1985 baseline survey of 7 to 15 years olds and included age, sex, state of residence, body mass index, smoking status, alcohol consumption status and measures of cardiorespiratory and muscular fitness (time on 1.6 km run, number of sit ups in 5 minutes, standing long jump). See methods for details.

Confounders included in all models were baseline measures of sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-15. Sensitivity analysis of applying inverse probability weighting in analyses of the association between alcohol consumption and triglycerides

Outcomes	Multiple imputation	Inverse probability weighting		
Triglycerides		Unweighted	Weighted with adult variables*	Weighted with childhood variables†
	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)
0g	-0.01 (-0.11, 0.10)	-0.04 (-0.16, 0.07)	-0.03 (-0.12, 0.07)	-0.03 (-0.14, 0.07)
>0-10g	Reference	Reference	Reference	Reference
>10-20g	-0.01 (-0.10, 0.08)	-0.03 (-0.13, 0.06)	-0.02 (-0.24, 0.09)	-0.02 (-0.15, 0.10)
>20-30g	-0.10 (-0.24, 0.06)	-0.09 (-0.25, 0.08)	-0.07 (-0.26, 0.11)	-0.08 (-0.26, 0.10)
>30g	-0.02 (-0.17, 0.13)	-0.06 (-0.23, 0.11)	-0.09 (-0.26, 0.07)	-0.02 (-0.23, 0.19)

* Adult variables for weights were from current follow-up in 2004-06 and included age, sex, education level, self-rated health, state of residence. See methods for details.

† Child variables for weights were from the 1985 baseline survey of 7 to 15 years olds and included age, sex, state of residence, body mass index, smoking status, alcohol consumption status and measures of cardiorespiratory and muscular fitness (time on 1.6 km run, number of sit ups in 5 minutes, standing long jump). See methods for details.

Confounders included in all models were baseline measures of sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-16. Sensitivity analysis of applying inverse probability weighting in analyses of the association between alcohol consumption and HDL cholesterol

Outcomes	Multiple imputation	Inverse probability weighting		
HDL cholesterol		Unweighted	Weighted with adult variables*	Weighted with childhood variables†
	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)
0g	-0.06 (-0.10, -0.01)	-0.07 (-0.11, -0.02)	-0.07 (-0.11, -0.02)	-0.07 (-0.12, -0.02)
>0-10g	Reference	Reference	Reference	Reference
>10-20g	0.09 (0.06, 0.13)	0.11 (0.07, 0.15)	0.12 (0.08, 0.16)	0.10 (0.06, 0.14)
>20-30g	0.20 (0.14, 0.26)	0.20 (0.13, 0.26)	0.19 (0.13, 0.25)	0.19 (0.13, 0.26)
>30g	0.22 (0.16, 0.28)	0.23 (0.17, 0.29)	0.22 (0.14, 0.31)	0.22 (0.14, 0.30)

* Adult variables for weights were from current follow-up in 2004-06 and included age, sex, education level, self-rated health, state of residence. See methods for details.

† Child variables for weights were from the 1985 baseline survey of 7 to 15 years olds and included age, sex, state of residence, body mass index, smoking status, alcohol consumption status and measures of cardiorespiratory and muscular fitness (time on 1.6 km run, number of sit ups in 5 minutes, standing long jump). See methods for details.

Confounders included in all models were baseline measures of sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-17. Sensitivity analysis of applying inverse probability weighting in analyses of the association between alcohol consumption and systolic blood pressure

Outcomes	Multiple imputation	Inverse probability weighting		
Systolic blood pressure		Unweighted	Weighted with adult variables*	Weighted with childhood variables†
	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)
0g	-0.14 (-1.60, 1.33)	-0.20 (-1.79, 1.40)	0.19 (-1.44, 1.83)	0.30 (-1.50, 2.10)
>0-10g	Reference	Reference	Reference	Reference
>10-20g	0.14 (-1.07, 1.36)	-0.03 (-1.31, 1.26)	0.05 (-1.34, 1.43)	0.37 (-1.11, 1.85)
>20-30g	1.02 (-1.12, 3.16)	0.91 (-1.33, 3.15)	1.12 (-1.25, 3.49)	1.25 (-1.16, 6.19)
>30g	3.01 (0.90, 5.12)	2.76 (0.49, 5.02)	3.01 (-0.08, 6.10)	2.98 (-0.22, 6.19)

* Adult variables for weights were from current follow-up in 2004-06 and included age, sex, education level, self-rated health, state of residence. See methods for details.

† Child variables for weights were from the 1985 baseline survey of 7 to 15 years olds and included age, sex, state of residence, body mass index, smoking status, alcohol consumption status and measures of cardiorespiratory and muscular fitness (time on 1.6 km run, number of sit ups in 5 minutes, standing long jump). See methods for details.

Confounders included in all models were baseline measures of sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-18. Sensitivity analysis of applying inverse probability weighting in analyses of the association between alcohol consumption and diastolic blood pressure

Outcomes	Multiple imputation	Inverse probability weighting		
Diastolic blood pressure		Unweighted	Weighted with adult variables*	Weighted with childhood variables†
	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)
0g	0.75 (-0.46, 1.96)	1.22 (-0.10, 2.53)	1.46 (0.07, 2.85)	1.58 (0.07, 3.09)
>0-10g	Reference	Reference	Reference	Reference
>10-20g	-0.14 (-1.14, 0.86)	-0.11 (-1.16, 0.95)	-0.09 (-1.22, 1.04)	-0.08 (-1.27, 1.11)
>20-30g	1.19 (-0.58, 2.96)	0.87 (-0.97, 2.72)	0.95 (-0.91, 2.82)	1.60 (-0.24, 3.44)
>30g	2.07 (0.33, 3.81)	1.77 (-0.10, 3.63)	1.88 (-0.64, 4.41)	2.08 (-0.45, 4.61)

* Adult variables for weights were from current follow-up in 2004-06 and included age, sex, education level, self-rated health, state of residence. See methods for details.

† Child variables for weights were from the 1985 baseline survey of 7 to 15 years olds and included age, sex, state of residence, body mass index, smoking status, alcohol consumption status and measures of cardiorespiratory and muscular fitness (time on 1.6 km run, number of sit ups in 5 minutes, standing long jump). See methods for details.

Confounders included in all models were baseline measures of sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-19. Sensitivity analysis of applying inverse probability weighting in analyses of the association between alcohol consumption and glucose

Outcomes		Multiple imputation	Inverse probability weighting		
Glucose			Unweighted	Weighted with adult variables*	Weighted with childhood variables†
		$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)
	0g	-0.01 (-0.06, 0.05)	-0.01 (-0.07, 0.07)	0.01 (-0.08, 0.11)	-0.01 (-0.10, 0.07)
	>0-10g	Reference	Reference	Reference	Reference
	>10-20g	0.01 (-0.05, 0.05)	-0.01 (-0.06, 0.05)	-0.01 (-0.06, 0.05)	0.01 (-0.04, 0.07)
	>20-30g	0.03 (-0.05, 0.12)	0.03 (-0.07, 0.12)	-0.01 (-0.08, 0.08)	0.02 (-0.07, 0.11)
	>30g	0.04 (-0.04, 0.12)	0.04 (-0.06, 0.13)	0.03 (-0.07, 0.13)	0.03 (-0.07, 0.13)

* Adult variables for weights were from current follow-up in 2004-06 and included age, sex, education level, self-rated health, state of residence. See methods for details.

† Child variables for weights were from the 1985 baseline survey of 7 to 15 years olds and included age, sex, state of residence, body mass index, smoking status, alcohol consumption status and measures of cardiorespiratory and muscular fitness (time on 1.6 km run, number of sit ups in 5 minutes, standing long jump). See methods for details.

Confounders included in all models were baseline measures of sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-20. Sensitivity analysis of applying inverse probability weighting in analyses of the association between alcohol consumption and prevalence of metabolic syndrome

	Multiple imputation	Inverse probability weighting		
Outcomes		Unweighted	Weighted with adult variables*	Weighted with childhood variables†
Prevalence MetS	$PR_{adjusted}$ (95% CI)	$PR_{adjusted}$ (95% CI)	$PR_{adjusted}$ (95% CI)	$PR_{adjusted}$ (95% CI)
0g	1.41 (0.90, 2.21)	1.17 (0.68, 2.01)	1.24 (0.70, 2.20)	1.00 (0.55, 1.81)
>0-10g	Reference	Reference	Reference	Reference
>10-20g	0.64 (0.41, 0.99)	0.57 (0.33, 0.97)	0.53 (0.30, 0.93)	0.60 (0.33, 1.08)
>20-30g	0.45 (0.17, 1.21)	0.42 (0.14, 1.25)	0.26 (0.07, 1.02)	0.31 (0.10, 1.03)
>30g	0.72 (0.36, 1.43)	0.94 (0.47, 1.89)	1.00 (0.48, 2.09)	1.05 (0.52, 2.12)

* Adult variables for weights were from current follow-up in 2004-06 and included age, sex, education level, self-rated health, state of residence. See methods for details.

† Child variables for weights were from the 1985 baseline survey of 7 to 15 years olds and included age, sex, state of residence, body mass index, smoking status, alcohol consumption status and measures of cardiorespiratory and muscular fitness (time on 1.6 km run, number of sit ups in 5 minutes, standing long jump). See methods for details.

Confounders included in all models were sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-21. Sensitivity analysis of applying inverse probability weighting in analyses of the association between alcohol consumption and continuous metabolic syndrome risk score

		Multiple imputation	Inverse probability weighting		
Outcomes			Unweighted	Weighted with adult variables*	Weighted with childhood variables†
CMSy		$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)	$\beta_{adjusted}$ (95% CI)
	0g	0.08 (-0.03, 0.17)	0.09 (-0.02, 0.19)	0.11 (-0.01, 0.23)	0.12 (-0.01, 0.25)
	>0-10g	Reference	Reference	Reference	Reference
	>10-20g	-0.09 (-0.17, -0.01)	-0.11 (-0.20, -0.03)	-0.12 (-0.21, -0.03)	-0.08 (-0.18, 0.01)
	>20-30g	-0.13 (-0.27, 0.01)	-0.14 (-0.29, 0.01)	-0.14 (-0.28, -0.01)	-0.13 (-0.28, 0.03)
	>30g	-0.08 (-0.21, 0.06)	-0.12 (-0.27, 0.04)	-0.12 (-0.29, 0.06)	-0.10 (-0.08, 0.16)

* Adult variables for weights were from current follow-up in 2004-06 and included age, sex, education level, self-rated health, state of residence. See methods for details.

† Child variables for weights were from the 1985 baseline survey of 7 to 15 years olds and included age, sex, state of residence, body mass index, smoking status, alcohol consumption status and measures of cardiorespiratory and muscular fitness (time on 1.6 km run, number of sit ups in 5 minutes, standing long jump). See methods for details.

Confounders included in all models were sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-22. Sensitivity analysis of the association between alcohol consumption and continuous metabolic syndrome risk score and components of metabolic syndrome using non-drinkers as the reference category

Outcome	Exposure Alcohol per day	All participants		Excluding those with an alcohol dependence	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}
Continuous MetS risk score	0g	Reference		Reference	
	>0-10g	-0.13 (-0.22, -0.03)	<0.01	-0.06 (-0.16, 0.05)	0.272
	>10-20g	-0.25 (-0.35, -0.14)	<0.001	-0.12 (-0.24, 0.00)	0.059
	>20-30g	-0.30 (-0.46, -0.15)	<0.001	-0.20 (-0.37, -0.03)	<0.05
	>30g	-0.17 (-0.32, -0.02)	<0.05	-0.15 (-0.32, 0.03)	0.095
Waist circumference	0g	Reference		Reference	
	>0-10g	-1.73 (-3.33, -0.13)	<0.05	-1.56 (-3.15, 0.03)	0.054
	>10-20g	-0.92 (-2.73, 0.89)	0.317	-1.96 (-3.79, -0.12)	<0.05
	>20-30g	-1.02 (-3.70, 1.65)	0.454	-2.22 (-4.84, 0.41)	0.098
	>30g	1.15 (-1.47, 3.76)	0.390	-2.23 (-4.84, 0.38)	0.095
Triglycerides	0g	Reference		Reference	
	>0-10g	-0.02 (-0.12, 0.08)	0.739	0.03 (-0.08, 0.14)	0.639
	>10-20g	0.07 (-0.05, 0.18)	0.245	0.03 (-0.09, 0.16)	0.614
	>20-30g	-0.01 (-0.18, 0.16)	0.898	-0.07 (-0.26, 0.11)	0.427

Outcome	Exposure Alcohol per day	All participants		Excluding those with an alcohol dependence	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>30g	0.10 (-0.07, 0.27)	0.269	-0.03 (-0.16, 0.21)	0.772
HDL cholesterol	0g	Reference		Reference	
	>0-10g	0.04 (0.01, 0.08)	<0.05	0.07 (0.02, 0.11)	<0.01
	>10-20g	0.08 (0.04, 0.13)	<0.001	0.15 (0.10, 0.20)	<0.001
	>20-30g	0.18 (0.10, 0.25)	<0.001	0.26 (0.19, 0.33)	<0.001
	>30g	0.16 (0.09, 0.23)	<0.001	0.28 (0.21, 0.36)	<0.001
Systolic BP	0g	Reference		Reference	
	>0-10g	1.02 (-0.56, 2.59)	0.207	0.24 (-1.38, 1.86)	0.773
	>10-20g	3.53 (1.73, 5.33)	<0.001	0.71 (-1.17, 2.59)	0.458
	>20-30g	4.57 (1.86, 7.28)	<0.01	0.79 (-1.90, 3.48)	0.566
	>30g	7.54 (4.9, 10.2)	<0.001	2.53 (-0.14, 5.21)	0.064
Diastolic BP	0g	Reference		Reference	
	>0-10g	-0.61 (-1.76, 0.54)	0.300	-1.16 (-2.48, 0.15)	0.083
	>10-20g	-0.05 (-1.36, 1.26)	0.936	-1.09 (-2.61, 0.43)	0.159
	>20-30g	1.19 (-0.78, 3.16)	0.235	-0.31 (-2.49, 1.88)	0.784
	>30g	3.25 (1.33, 5.16)	<0.01	0.35 (-1.82, 2.53)	0.752

Outcome	Exposure Alcohol per day	All participants		Excluding those with an alcohol dependence	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}
Glucose	0g	Reference		Reference	
	>0-10g	0.03 (-0.03, 0.09)	0.305	-0.01 (-0.08, 0.05)	0.681
	>10-20g	0.09 (0.02, 0.15)	<0.05	0.01 (-0.07, 0.08)	0.956
	>20-30g	0.14 (0.03, 0.24)	<0.01	0.01 (-0.10, 0.12)	0.844
	>30g	0.18 (0.08, 0.27)	<0.001	0.03 (-0.07, 0.14)	0.560

Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Table 3-23. Sensitivity analysis of the association between alcohol consumption and prevalence of metabolic syndrome using non-drinkers as the reference category

Outcome	All participants		Excluding those with an alcohol dependence	
Prevalence MetS	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
Alcohol per day				
0g	Reference		Reference	
>0-10g	0.86 (0.56, 1.33)	0.493	0.76 (0.47, 1.24)	0.272
>10-20g	0.65 (0.38, 1.11)	0.116	0.47 (0.25, 0.87)	<0.05
>20-30g	0.42 (0.15, 1.18)	0.100	0.33 (0.11, 0.99)	<0.05
>30g	0.90 (0.43, 1.87)	0.774	0.52 (0.23, 1.15)	0.104

Abbreviation: MetS=metabolic syndrome; PR=prevalence ratios; CI=confidence interval.

Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness and depression and anxiety

Chapter 4

Patterns of alcohol consumption, carotid intima-media thickness and insulin resistance in young adults

4 Chapter 4. Patterns of alcohol consumption, carotid intima-media thickness and insulin resistance in young adults

4.1. Introduction

There is conflicting evidence regarding associations between the types of alcohol consumed and cardio-metabolic health. Some authors have shown that the prevalence of MetS was lower for alcohol consumers than that for non-drinkers based on their total amount of alcohol consumption and irrespective of the type of beverage consumed [124]. Others showed that the overall metabolic profile of people that consume mostly wine was better than that of individuals who consumed other types of alcoholic beverages [211]. One difficulty with such studies is how to account for the fact that people typically drink several types of alcohol [47]. Just as the examination of dietary patterns compared to total energy intake has provided insights into links between diet and health outcomes [223], identifying individuals into alcohol consumption patterns based on types of alcohol consumed has the potential to provide novel insights into associations between alcohol consumption and cardio-metabolic health.

There have been few studies in younger people of alcohol consumption and pre-clinical markers of cardiovascular and metabolic diseases, such as carotid intima-media thickness (IMT) [224] or IR [225]. We recently found that total alcohol consumption was associated with several cardiovascular risk factors, including high BP, lipid abnormalities and central obesity that are pre-cursors to carotid IMT and IR [160]. We found that these associations were confounded by social-demographic factors, other lifestyle behaviours and mental health. Other researchers have shown a linear association between higher alcohol consumption and elevated carotid IMT even in a relatively young population of 24–39 years old [121]. Authors from one cross-sectional investigation reported a negative association between alcohol consumption and IR in young adults [203]. It has not been established whether overall patterns of alcohol consumption, including both the quantity and type of beverages consumed, influences the relation between alcohol and carotid IMT and IR.

The aims of the present study were to: (1) examine the patterns of alcohol consumption in terms of both quantities and types of alcohol consumed and the demographic correlates of these; (2) examine the associations between patterns of alcohol consumption identified and

carotid IMT and IR; and (3) examine whether detailed patterns of alcohol consumption show different associations with carotid IMT and IR than self-reported quantities of alcohol consumption alone using model fit and discrimination measures.

4.2. Methods

The present study was a cross-sectional analysis of data collected from the 2004–2006 follow-up of the CDAH study that began as the 1985 ASHFS. The 1985 study comprised a nationally representative sample of school children aged 7–15 years. A detailed description of the cohort has been published elsewhere [204]. The flow of participants from baseline to follow-up is described in Figure 4-1.

4.2.1. Measurement of primary exposure

We collected information regarding alcohol consumption from a FFQ at the first follow-up (herein referred to as the present study) when participants were 26–36 years old. Frequency of intake (options: never or <1/month, 1–3 times/month, once/week, 2–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–5 times/day and >6 times/day) of alcoholic beverages (options: light, medium or full strength beer; red, white and sparkling wine; wine cooler; spirits/liqueurs; spirit-based mixed drinks; sherry/port and other) over the last 12 months was reported. The estimated amount of alcohol consumed per day for each type of beverage was determined by multiplying the frequency of drinking by the estimated grams of pure alcohol for each beverage type (1 standard drink was equivalent to 10 g of pure alcohol consumed). The total amount of alcohol consumed per day was defined as the sum of the amount of alcohol consumed for each type of beverage [174]. Self-reported alcohol intake by FFQ has been shown to be a reliable and valid instrument in young adults [16].

A sub-sample of 2,170 participants (97.7% of the total sample) had a 12-month DSM-IV-based AUD diagnosis (e.g. alcohol dependence and/or alcohol abuse) based on the CIDI [205].

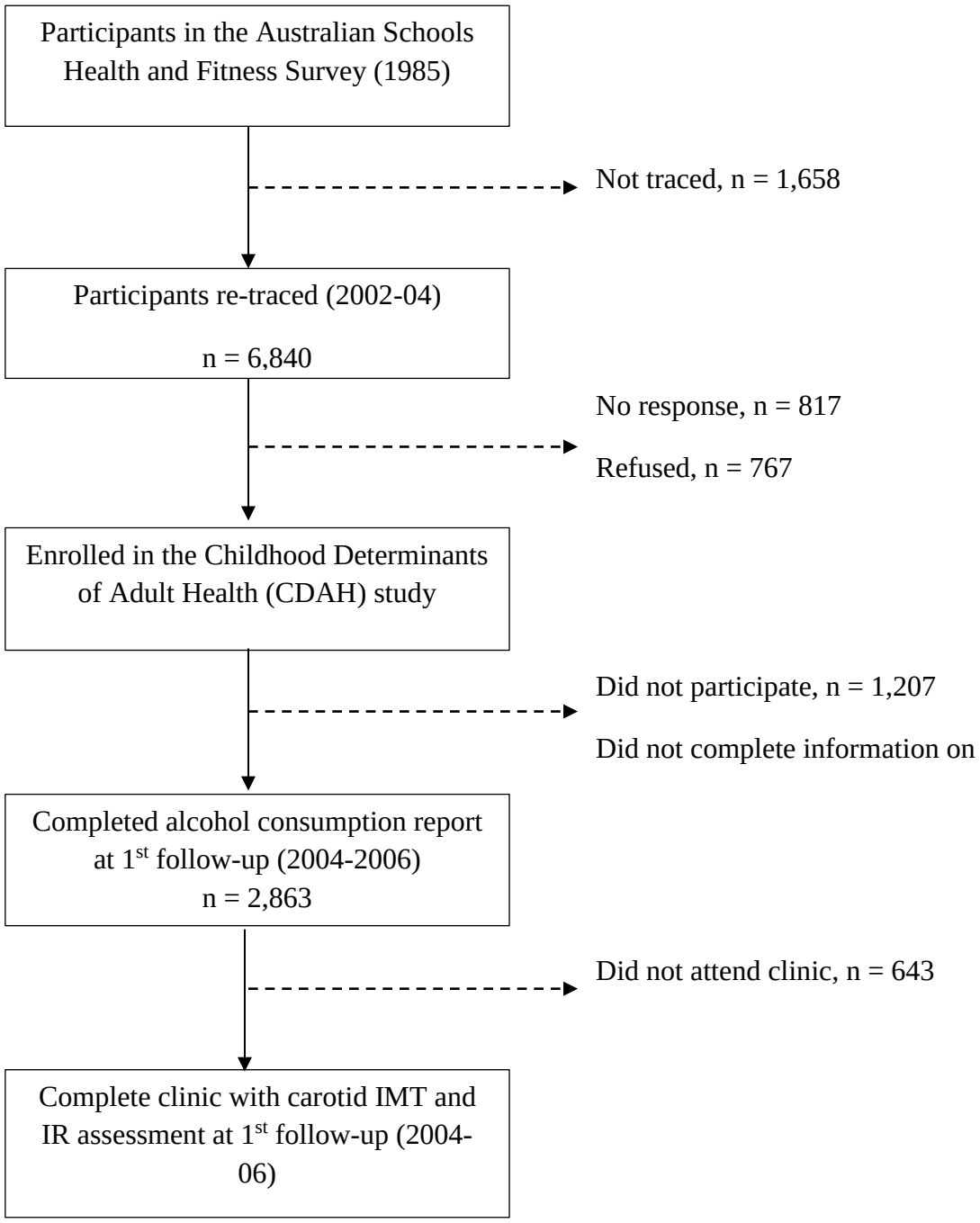


Figure 4-1. Flow chart of alcohol consumption status and alcohol-related outcomes during follow-up periods

4.2.2. Measurement of outcomes

The primary outcomes were IR and carotid IMT. IR was estimated by the HOMA-IR index, a robust tool for the surrogate assessment of IR developed by Matthews et al. [226], calculated using the following formula: fasting serum insulin (U/mL) × fasting glucose (mmol/L)/22.5 [227]. B-mode ultrasound studies of the carotid artery were performed using a portable Acuson Cypress ultrasound with a 7.0 MHz linear-array transducer following a previously reported standardised protocol [228]. Mean values were used in the analysis. In most studies, dichotomous high carotid IMT and high HOMA-IR were defined as ≥ 90th percentile being the optimal cut-off values [121, 229]. We also defined high carotid IMT as a maximum IMT ≥ 90th percentile and high HOMA-IR as a HOMA index ≥ 90th percentile for age and sex specific values as dichotomous outcomes.

4.2.3. Covariates

The following covariates were considered: age, sex, SES quartile based on area of residence, region, education level, occupation, marital status and smoking status measured by questionnaires; physical activity determined by the IPAQ [181]; CRF estimated as PWC [182]; dietary intake assessed using a FFQ; and depression and anxiety from the aforementioned CIDI [205]. Those variables were selected as they are strongly associated with alcohol consumption [74, 76] and the cardio-metabolic outcomes of interest [115, 230].

4.2.4. Statistical analysis

We used the latent class analysis (LCA) to quantify the overall patterns of alcohol consumption. The model class in the present study was based on original measures of total amount consumed (g/day) of each type of alcoholic beverages (beer, wine and spirits) and categorised as per above. The model fit was assessed based on three sets of criteria: 1) Lo-Mendel-Rubin likelihood ratio test where low p-values (<0.05) indicate there are significant improvements in model fit from the inclusion of an additional class; 2) Bayesian information criteria (BIC) and Akaike's information criteria (AIC) statistics, with lower values indicating better model fit and 3) entropy, ranging from 0 to 1, which is a measure of the clarity of classification (values close to 1 indicate clear classification). Latent class analyses were performed using the Mplus version 7 software program.

Comparisons of characteristics by the latent classes identified were examined using t-tests or $\chi 2$ tests. Multinomial regression with the alcohol consumption patterns as the outcome and potential covariates was used to examine the characteristics associated with the alcohol consumption patterns identified.

We then examined the association between alcohol consumption classified as (1) patterns according to latent classes identified and (2) total alcohol consumed per day against dichotomous cardio-metabolic outcomes (HOMA-IR and carotid IMT) using multivariable log binomial regression (PR and 95% CIs), and with continuous cardio-metabolic outcomes using multivariable linear regression (β coefficients and 95% CIs). All models examining the associations between alcohol consumption patterns and outcomes were presented as unadjusted and adjusted for the confounding factors specified above, based on purposeful model building procedures [208]. We performed further sensitivity analyses by excluding those participants who were diagnosed with an AUD at the time of the study to rule out the possibility of reverse causation. There was no evidence of the effect of modification by sex on the associations between alcohol consumption and the outcomes; therefore, the results for men and women are presented together.

To examine the utility of patterns of alcohol consumption compared with total alcohol consumption we compared the model calibrations (the fit of the predicted values produced by the model compared to the actual observed values of the outcome) by deviance in log binomial regressions against cardio-metabolic outcomes. We also examined subject discrimination (the capacity of the model to correctly classify those who develop the outcome and those who do not) using the area under the curve (AUC) receiver operating characteristics between the two measurements of alcohol consumption.

We handled missing data from baseline to follow-up using a combination of IPW and MI [231]. MI using chained equations with 30 estimations was applied to replace missing data of covariates. The non-missing variables used for imputations were sex, age and type of school at the baseline in 1985. Weights for IPW were based on the inverse of the probability of providing baseline data given variables from 1985 (e.g. age, sex, smoking, state of residence, type of school, father's education, mother's education and scholastic level assigned by school). The threshold for significance was $p \leq 0.05$ (two-tailed). Analyses were performed with the Stata 12.0 software program.

4.3. Results

4.3.1. Sample characteristics

A total of 2,220 participants (mean age=29.3 years, SD=2.5) were included in the final analyses, almost half were men (48%), had primarily graduated from tertiary or higher education (43%), were working as managers or professionals (55%), and were married or living as married (69%). More than one-third (32%) of participants reported drinking alcohol when they were aged 9–15 years old. Meanwhile, almost a quarter were current smokers (22%), 12% of the sample were classified with an AUD, including alcohol dependence (7.5%) and/or alcohol abuse (6.7%), and 16% had been diagnosed with depression and/or anxiety using the CIDI.

4.3.2. Model selection for drinking patterns

Model fit statistics for the 2–6-class solutions without covariates are presented in Table 4-1. While the AIC was slightly lower for the 3-class solution than for the 2-class solution (14,810 vs 14,833), the BIC, LMR chi-square and entropy all favoured a larger class solution. Comparing the 3- and 4-class solutions, the AIC was almost identical, the BIC favoured the 3-class solution (14,930 vs 14,975), and the chi-square did not favour either solution (p=0.577 vs p=0.727). Although the evidence did not unequivocally support the 3-class solution over the 4-class solution, the 4-class solution did not indicate the existence of an additional, substantive class over the more parsimonious 3-class solution; there were only six individuals assigned to the 4-class solution, and this solution was not very stable as it changed drastically when covariates were added. Thus, the 3-class solution was chosen as the most parsimonious, best-fitting model (Table 4-1).

Table 4-1. Model fit of latent class analysis ǂ

	Criteria 1		Criteria 2		Criteria 3
	LMR CS	p-value	AIC	BIC	Entropy
From 3-categorical inputs					
1-Class	-	-	15266.146	15301.903	-
2-Class	438.789	<0.0001	14833.481	14910.957	0.701
3-Class	35.895	0.001	14810.834	14930.027	0.577
4-Class	9.959	0.074	14814.697	14975.607	0.727

ǂ - 5 and 6 class solutions were conducted but not reported as there were indications of model non-identification

4.3.3. Latent class probability and class definitions

The conditional response probabilities by class are show in Figure 4.2. For the 3-class solution, the most prevalent class (n=1,673, 73.7%) was characterised by a moderate probability of having approximately one drink/day of all types (beer, wine and spirits) on average and a low likelihood of consuming more than one drink/day—named as ‘moderate beer, wine and spirits’ consumers (median interquartile range [IQR] total alcohol consumed: 6.3 [3.0–10.7] g/day). The second prevalent class (n=297, 15.4%) was characterised by a low probability of consuming any alcohol, named as the ‘none/light’ consumer group (median [IQR] total alcohol consumed: 0.1 [0–0.5] g/day). The last class (n=250, 10.8%) was characterised by a moderate probability of having approximately one drink/day of all types (beer, wine and spirits) on average and moderate probability of consuming more than one drink/day of beer (but not so for wine or spirits), labelled as a ‘moderate wine and heavy beer’ consumer group (median [IQR] total alcohol consumed: 24.4 [17.2–41.3] g/day; median [IQR] total beer consumed: 15.0 [11.8–37.5] g/day) (Figure 4-2).

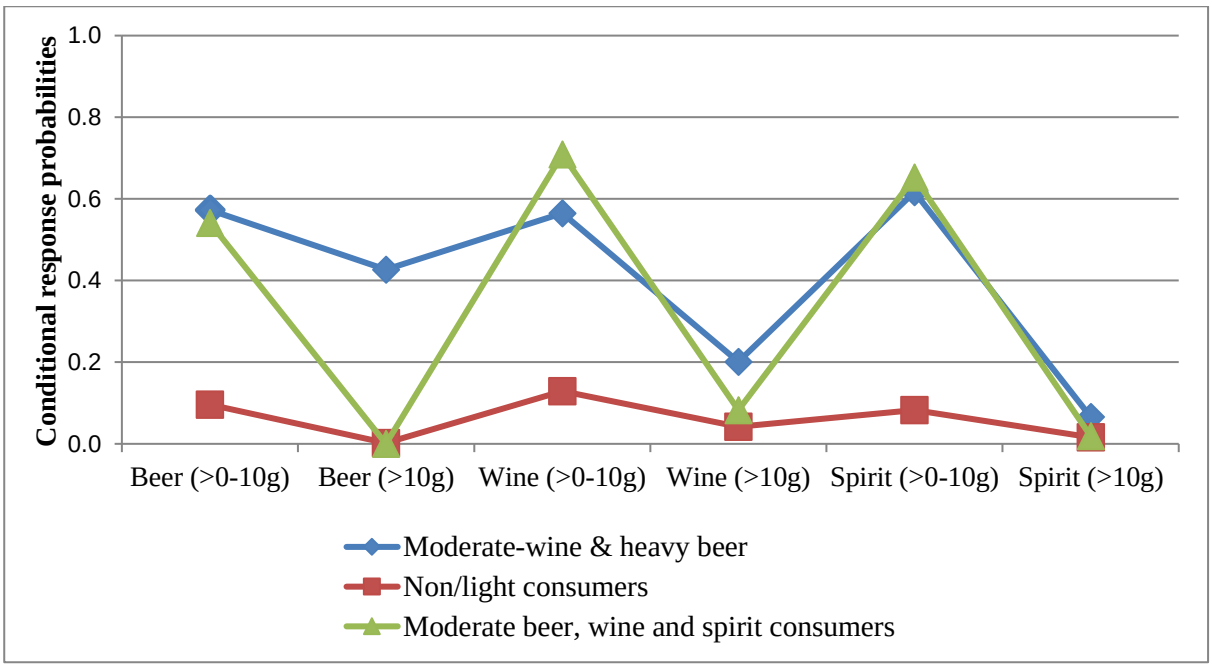


Figure 4-2. Conditional response probabilities for 3-class solution

Compared to 'moderate beer, wine and spirits' consumers, those in the 'none/light' consumer group were less often male, less likely to be current smokers, and less likely to be classified as an AUD, had a higher DGI score, had a higher physical HRQoL score and a higher mental HRQoL score at 26–36 years of age. In contrast, 'none/light' consumers were more likely to be living in a low SES postcode, more often married and had a higher prevalence of depression and/or anxiety compared to those were 'moderate beer, wine and spirits' consumers. There were differences between the 'moderate wine and heavy beer' group compared to the others. They were much more often male, more likely to be classified as an AUD, more likely to be a current smoker, and consumed more total alcohol and total beer on average (Table 4-2). Similar characteristics of clinical biomarkers were observed between the three classes identified (Appendix Table 4-8).

Table 4-2. Characteristics of the study population by latent class (N=2,220)

		Class 1: None/light consumers (n=297)	Class 2: Moderate beer, wine and spirit consumers (n=1,673)	Class 3: Moderate-wine & heavy beer consumers (n=250)	P_{value}
Sex, n (%)	Male	95 (32)	752 (45)	209 (84)	<0.001
Age (years)	Mean (SD)	29.5 (2.4)	29.3 (2.6)	29.2 (2.6)	0.529
Region, n (%)	Major cities	207 (70)	1,304 (78)	187 (75)	<0.05
	Inner region	59 (20)	246 (15)	41 (16)	
	Outer regional	26 (9)	111 (7)	21 (8)	
	Remote	5 (2)	11 (1)	1 (1)	
Education, n (%)	Tertiary	117 (39)	758 (45)	84 (34)	<0.01
	Vocational	97 (33)	490 (29)	91 (36)	
	School only	83 (28)	420 (25)	75 (30)	
SES, n (%)	Quartiles 1	91 (31)	347 (21)	55 (22)	<0.001
	Quartiles 2	74 (25)	393 (24)	64 (26)	
	Quartiles 3	78 (26)	420 (25)	59 (24)	
	Quartiles 4	54 (18)	512 (31)	72 (29)	
Occupation, n (%)	Professionals	126 (43)	944 (57)	126 (51)	<0.001
	White collar	58 (20)	301 (18)	28 (11)	
	Blue collar	38 (13)	259 (16)	80 (33)	
	Unemployed	73 (25)	144 (9)	11 (5)	
Marital status, n (%)	Married/de facto	216 (73)	1,133 (68)	171 (68)	0.120
	Single	71 (24)	479 (29)	76 (30)	
	Divorced/	10 (3)	61 (4)	3 (1)	

		Class 1: None/light consumers (n=297)	Class 2: Moderate beer, wine and spirit consumers (n=1,673)	Class 3: Moderate-wine & heavy beer consumers (n=250)	P_{value}
	Separated				
Total alcohol consumed	gm/day	0.5 (5.1)	8.1 (7.8)	33.3 (23.6)	<0.001
Total beer	gm/day	0.0 (0.0)	2.2 (2.6)	22.5 (19.2)	<0.001
Total wine	gm/day	0.0 (0.0)	4.4 (7.0)	6.9 (13.3)	<0.001
Total spirits	gm/day	0.5 (5.1)	1.4 (2.0)	4.0 (6.6)	<0.001
Total physical activity	mins/week	694 (520)	768 (509)	858 (525)	<0.01
Daily steps	10000 steps	0.8 (0.3)	0.9 (0.3)	1.0 (0.3)	<0.001
PWC_{170}	Mean (SD)	-9.0 (32.5)	1.5 (35.1)	2.2 (38.2)	<0.001
Dietary (DGI)	Mean (SD)	101 (20)	103 (19)	88 (18)	<0.001
DGI excluding alcohol	Mean (SD)	91 (20)	94 (19)	83 (17)	<0.001
Physical HRQoL	Mean (SD)	51.3 (8.1)	52.7 (6.2)	53.1 (5.9)	<0.01
Mental HRQoL	Mean (SD)	48.9 (9.7)	49.8 (8.7)	51.0 (8.1)	<0.01
AUDs prevalence, n (%)	Positive	6 (2)	171 (11)	76 (33)	<0.001
Drink at childhood, n (%)	Positive	59 (25)	427 (33)	80 (40)	<0.01
Smoking prevalence, n (%)	Positive	32 (11)	372 (22)	86 (34)	<0.001
Depression/anxiety, n (%)	Positive	54 (20)	242 (16)	25 (11)	<0.05
History of CVD, n (%)	Positive	29 (10)	167 (11)	41 (18)	<0.01
Antidepressant medications, n (%)	Positive	18 (7)	72 (5)	7 (3)	0.155

Data are shown as Number (Percentage) for categorical variables and as Mean (SD) for continuous variables; SES=socioeconomic status; PA=physical activity; PWC_{170}= physical work capacity; DGI=Dietary Guideline Index; BMI=body mass index; AUDs=Alcohol use

disorders; AD=Alcohol dependence; AB=Alcohol abuse MetS=metabolic syndrome; HRQoL=health-related quality of life.

4.3.4. Association between patterns of alcohol consumption and cardio-metabolic risk factors

Multivariable models examining alcohol consumption and each cardio-metabolic risk factor are presented in Table 4-3. In the unadjusted model, compared to 'none/light' consumers, 'moderate beer, wine and spirits' consumers had a significantly lower HOMA-IR and a significantly higher carotid IMT. Similar results were observed for 'moderate wine and heavy beer' consumers in comparison to 'none/light' consumers. These results did not persist in the adjusted models (Table 4-3). For total alcohol consumption, those who consumed 30 g of pure alcohol per day or more on average were associated with significantly lower HOMA-IR than those who consumed light amounts of alcohol (>0–10 g/day). The result persisted after adjusting for covariates (Table 4-3).

Table 4-4 shows the association between patterns of alcohol consumption and prevalence of high IMT and high HOMA-IR. In the unadjusted model, 'moderate beer, wine and spirits' consumers had a significant lower prevalence of elevated HOMA-IR and had a non-significant lower prevalence of elevated carotid IMT, whereas 'moderate wine and heavy beer' consumers had a significantly lower prevalence of elevated HOMA-IR and had a non-significant lower prevalence of elevated carotid IMT. These results did not remain significant in the adjusted models (Table 4-4). For total alcohol consumption, only moderate drinking (>10–20 g/day) was associated with significant lower prevalence of elevated HOMA-IR than that of light drinking (>0–10 g/day) after adjusting for covariates (Table 4-4).

Table 4-3. Multivariable linear regression analysis of the association between alcohol consumption by patterns and total amounts per day consumed and HOMA-IR and carotid IMT (N=2,220)

Outcome	Exposure	Unadjusted		Adjusted	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}
HOMA-IR	Drinking patterns				
	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	-0.15 (-0.28, -0.02)	<0.05	-0.01 (-0.17, 0.14)	0.897
	Moderate-wine & heavy beer consumers	-0.26 (-0.42, -0.10)	<0.01	-0.13 (-0.34, 0.08)	0.233
	Amounts per day				
	0g	0.11 (-0.03, 0.24)	0.115	-0.03 (-0.19, 0.13)	0.744
	>0-10g	Reference		Reference	
	>10-20g	-0.14 (-0.23, -0.05)	<0.01	-0.12 (-0.24, 0.01)	0.051
	>20-30g	-0.10 (-0.25, 0.05)	0.174	-0.01 (-0.24, 0.22)	0.923
	>30g	-0.25 (-0.40, -0.10)	<0.01	-0.25 (-0.45, -0.06)	<0.05
Carotid-IMT	Drinking patterns				
	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.01 (0.001, 0.02)	<0.05	0.02 (-0.03, 0.07)	0.398
	Moderate-wine & heavy beer consumers	0.02 (0.01, 0.03)	<0.05	-0.01 (-0.08, 0.06)	0.788
	Amounts per day				
	0g	-0.01 (-0.02, -0.001)	<0.05	-0.03 (-0.07, 0.02)	0.296
	>0-10g	Reference		Reference	
	>10-20g	0.001 (-0.01, 0.01)	0.908	-0.03 (-0.07, 0.01)	0.061
	>20-30g	0.001 (-0.02, 0.02)	0.923	-0.03 (-0.08, 0.03)	0.370

	>30g	0.01 (-0.01, 0.02)	0.515	-0.03 (-0.10, 0.04)	0.404

β =regression coefficient; CI=confidence interval. Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

Table 4-4. Multivariable regression analysis of the association between alcohol consumption by patterns and total amounts per day consumed and prevalence of elevated HOMA and prevalence of elevated carotid IMT (N=2,220)

Outcome	Exposure	Unadjusted		Adjusted	
		PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
Prevalence of elevated HOMA	Drinking patterns				
	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.86 (0.55, 1.34)	0.506	1.12 (0.53, 2.36)	0.772
	Moderate-wine & heavy beer consumers	0.87 (0.45, 1.66)	0.663	1.00 (0.35, 2.87)	0.995
	Amounts per day				
	0g	1.85 (1.27, 2.69)	<0.01	1.09 (0.60, 1.98)	0.767
	>0-10g	Reference		Reference	
	>10-20g	0.44 (0.28, 0.68)	<0.001	0.38 (0.20, 0.73)	<0.01
	>20-30g	0.72 (0.33, 1.60)	0.422	1.06 (0.36, 3.13)	0.913
	>30g	0.46 (0.21, 1.03)	0.059	0.43 (0.14, 1.33)	0.144
Prevalence of elevated Carotid IMT	Drinking patterns				
	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.87 (0.53, 1.42)	0.577	1.36 (0.62, 2.98)	0.449
	Moderate-wine & heavy beer consumers	1.12 (0.58, 2.18)	0.738	1.71 (0.59, 4.90)	0.321
	Amounts per day	1.13 (0.72, 1.79)	0.592	0.88 (0.41, 1.86)	0.734

0g	Reference		Reference	
>0-10g	0.95 (0.62, 1.45)	0.813	0.81 (0.47, 1.39)	0.438
>10-20g	0.51 (0.19, 1.34)	0.169	0.51 (0.17, 1.56)	0.241
>20-30g	1.01 (0.09, 0.14)	0.989	1.35 (0.57, 3.18)	0.496
>30g	1.13 (0.72, 1.79)	0.592	0.88 (0.41, 1.86)	0.734

PR=prevalence ratio; CI=confidence interval. Adjusted for age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

4.3.5. Comparison of associations between patterns of alcohol consumption and total alcohol consumed against adult cardio-metabolic risk factors

For adult high carotid IMT and high HOMA-IR, AUC and deviance values were comparable between the patterns and total quantity measures (Appendix Table 4-14). AUC values were only moderate for each of the patterns as well as the quantity classification in the prediction of outcomes. Model goodness of fit as shown by the deviance in log binomial regression was acceptable for all models examined (Appendix Table 4-14).

4.4. Discussion

We examined the overall patterns of alcohol consumption among young adults. We found three dominant patterns of alcohol consumption, with the 'moderate beer, wine and spirits' consumers being the most prevalent drinking pattern. Our findings suggested that while higher levels of total alcohol consumption were significantly associated with lower IR, the most common pattern of alcohol consumption was not associated with carotid IMT or HOMA-IR after adjustment for socio-demographic, lifestyle and behavioural factors, and mental health conditions.

There were notable differences in alcohol consumption patterns by socio-demographic background and lifestyle behaviours. Our results showed that the pattern of 'moderate beer, wine and spirits' consumption was associated with a social background characterised by living in a higher SES postcode, having a higher level of occupation, more likely to be married, and more likely to be current smokers. The relationships among alcohol

consumption, the choice of types of alcoholic beverages such as wine, beer and spirits and other lifestyle behaviours with metabolic health have also been identified in previous studies in middle-age and older populations [232].

We found that higher amounts of total alcohol consumed per day were associated with lower prevalence of elevated HOMA-IR. This result is consistent with a previous finding in young adults [203]. In contrast, the alcohol consumption patterns were not associated with a risk of high carotid IMT or IR after adjustment for demographic factors, health behaviours, CRF, and mental health conditions that had not been examined in previous studies. This suggests that inadequate control for confounders might have led to an overestimation of the associations between alcohol consumption and elevated carotid IMT or IR in previous findings in young adults. Given the associations previously reported in older or the more general population [233] and with total alcohol consumption in the present study, the lack of an association between patterns of consumption and IMT or IR suggest that common components of different types of alcohol are responsible for the associations. The biological mechanisms underlying the association between alcohol consumption and IR are not known. Suggested possible mechanisms include the effect of alcohol on beta cells, hepatic glucose metabolism [234] or growth hormone [235]. Further studies are required to understand the underlying mechanisms.

The information on alcohol consumption patterns and the total amounts consumed were both associated with dichotomous outcomes of elevated carotid IMT and IR. However, information on alcohol consumption patterns did not provide greater utility than simply gathering information on frequency and quantity of alcohol in the prediction of outcomes. It appears that, unlike for diet [223], quantification of patterns did not provide additional model calibration and subject discrimination for cardio-metabolic outcomes in. Thus, either total consumption or consumption patterns would produce equivalent results in their association with each of these outcomes.

The modest associations between alcohol consumption, measured either with total consumption or patterns, and these cardio-metabolic outcomes once confounders were considered adds to recent evidence suggesting that the benefits of alcohol consumption for health may have been over-stated [117, 236]. Indeed, when coupled with evidence on the harms of heavier alcohol consumption, particularly binge drinking, to health, cardiovascular risks and diseases [237-239], recent suggestions to change alcohol consumption guidelines appear warranted. Nevertheless, the lack of consistent measures and definitions describing

binge drinking might contribute to the difficulty in identifying the drinking patterns that imply alcohol-cardio-metabolic disease relationships and may account partly for differences in previous findings between studies of alcohol consumption and its effect on various cardiovascular outcomes [237, 239, 240].

The present study used a large national sample of young Australians on whom standardised measurements were made with consideration of a range of study factors. The prevalence of current drinkers among young adults in the present study (86%) was equivalent to the findings from a national survey of the general population (83%) during the same period [47] which increases the generalisability of the results. There are also several limitations. The cross-sectional design of the present study limits the causal inferences concerning the relationships of alcohol consumption with carotid IMT and IR. We ruled out the possibility of reverse causation whereby participants with other health problems might stop drinking as a consequence at the time of the study by excluding those diagnosed with an AUD in the sensitivity analyses, showing small differences in the results (Appendix Table 4-15 and Table 4-16). We also had substantial loss to follow-up since childhood, which might affect the generalisability of our findings to other populations. However, a comparison of the study population (n=2,200) with data of participants lost to follow-up from the baseline showed that they had comparable characteristics in terms of socio-demographic factors and family background (Appendix Table 4-6). In addition, sensitivity analyses showed small differences after applying a combination of IPW and MI to deal with missing data from baseline to follow-up. Thus, the loss to follow-up does not appear to have had a great effect on our results. Another limitation was that, beyond the three classes identified, it is important to note a particular class that was absent from the latent class analyses of our sample—the ‘heavier drinkers’. The proportions of participants consuming 20 g/day or over for each type of beverage were low to allow us to examine the association between ‘heavier drinkers’ and the outcomes. This is notable in that heavy or risky drinking, irrespective of which type of alcoholic beverages were consumed, were identified as an important health risk factor in young people [241].

4.5. Conclusions

The most common pattern of drinking in our cohort of younger adults was consuming moderate amounts of several types of alcohol. While drinking moderate amounts of alcohol was, on average, associated with lower prevalence of elevated HOMA-IR, no association was found between the most common pattern of alcohol consumption in this cohort of young adults and carotid IMT and HOMA-IR after adjusting for covariates, including socio-demographic, lifestyle and behavioural factors, and mental health. The lack of association might contrast with apparent benefits of moderate alcohol consumption for cardio-metabolic health in older people. This may have implications for public health messages in that alcohol is neither good nor bad for cardio-metabolic health at these ages.

4.6. Appendix 4. Additional Tables and Figures

Table 4-5. Mean class assignment probability by class for 3-class solution (N=2,200)

	Moderate-wine & heavy beer	Non/light consumers	Moderate beer, wine and spirit consumers
Moderate-wine & heavy beer (n=250)	0.949	0.006	0.045
Non/light consumers (n=297)	0.000	0.877	0.123
Moderate beer, wine and spirit consumers (n=1,673)	0.165	0.083	0.752

Table 4-6. Baseline characteristics of the study population and participants lost to follow-up from baseline

Characteristics	Study population (N=2,220)		Loss to follow-up (N=6,278)		P-value
	n	% or Mean (S.D.)	N	% or Mean (S.D.)	
Male	1,056	48	3,251	52	0.001
Age, years	2,220	11.1 (2.5)	6,278	10.8 (2.6)	0.641
State of residence*					0.001
ACT	63	3	111	2	
NSW	646	29	2,311	37	
VIC	636	29	1,488	24	
QLD	383	17	1,107	18	
SA	205	9	503	8	
WA	194	9	507	8	
TAS	52	2	117	2	
NT	41	2	134	2	
Type of school					0.001
State	1,613	73	4,762	76	
Catholic	458	21	1,215	19	
Independent	149	6	301	5	
SES					0.001
Quartile 1	480	28	1,010	22	
Quartile 2	483	28	1,317	29	
Quartile 3	624	36	1,803	39	
Quartile 4	131	8	451	10	
Scholastic level					0.001

Characteristics	Study population (N=2,220)		Loss to follow-up (N=6,278)		P-value
	n	% or Mean (S.D.)	N	% or Mean (S.D.)	
Excellent	267	13	476	9	
Above average	694	33	1,517	26	
Average	833	40	2,446	41	
Below average	241	11	1,095	18	
Poor	45	2	347	5	
Father's education					0.004
Tertiary	485	23	112	18	
Vocational	666	32	195	31	
School only	911	44	316	50	
Mother's education					0.236
Tertiary	378	18	109	17	
Vocational	416	19	109	17	
School only	1,342	63	428	66	

*ACT, Australian Capital Territory; NSW, New South Wales; VIC, Victoria; QLD, Queensland; WA, Western Australia; TAS, Tasmania; NT, Northern Territory

Table 4-7. Characteristics of clinical biomarkers according to type of alcoholic beverages

	Total beer			P_{value}	Total wine			P_{value}	Total spirit			P_{value}
	0g	>0-10g	>10g		0g	>0-10g	>10g		0g	>0-10g	>10g	
	n=923	n=1,072	n=225		n=690	n=1,290	n=240		n=934	n=1,230	n=56	
Prevalence MetS	60 (6.5)	72 (6.7)	16 (7.1)	0.943	70 (10.1)	65 (5.0)	13 (5.4)	<0.001	60 (6.4)	83 (6.8)	5 (8.9)	0.755
Continuous MetS	0.08 (0.74)	-0.05 (0.68)	-0.05 (0.71)	<0.001	0.11 (0.76)	-0.04 (0.69)	-0.10 (0.65)	<0.001	-0.01 (0.71)	0.01 (0.70)	0.01 (0.84)	0.947
Waist	81.6 (13.3)	84.4 (11.5)	87.9 (11.1)	<0.001	86.2 (13.2)	82.8 (12.0)	80.4 (10.5)	<0.001	83.3 (12.5)	83.7 (12.1)	88.4 (15.1)	<0.01
Triglycerides	1.1 (0.8)	1.1 (0.8)	1.3 (0.9)	<0.01	1.2 (0.9)	1.1 (0.7)	1.1 (0.9)	<0.05	1.1 (0.7)	1.1 (0.8)	1.4 (1.2)	<0.05
HDL-C	1.4 (0.3)	1.4 (0.3)	1.5 (0.3)	<0.01	1.3 (0.3)	1.4 (0.3)	1.6 (0.4)	<0.001	1.4 (0.4)	1.4 (0.3)	1.5 (0.3)	0.651
Systolic BP	114 (12)	120 (12)	124 (12)	<0.001	119 (13)	117 (12)	118 (13)	<0.001	117 (13)	118 (12)	121 (14)	0.053
Diastolic BP	71 (9)	73 (9)	75 (10)	<0.001	73 (9)	72 (9)	73 (10)	<0.01	72 (9)	72 (9)	74 (10)	0.309
Glucose	4.9 (0.5)	5.0 (0.5)	5.2 (0.5)	<0.001	5.0 (0.5)	5.0 (0.4)	5.0 (0.5)	0.093	5.0 (0.5)	5.0 (0.5)	5.0 (0.4)	0.322
HOMA-IR	1.7 (1.3)	1.6 (1.0)	1.5 (1.3)	<0.05	1.8 (1.3)	1.6 (1.1)	1.4 (0.8)	<0.001	1.6 (1.1)	1.6 (1.2)	1.6 (1.0)	0.877
Carotid IMT	0.55 (0.07)	0.57 (0.09)	0.59 (0.09)	<0.05	0.56 (0.09)	0.56 (0.08)	0.57 (0.09)	0.539	0.56 (0.08)	0.56 (0.08)	0.56 (0.09)	0.925

Data are shown as Number (Percentage) for categorical variables and as Mean (SD) for continuous variables.

MetS=metabolic syndrome; BP=blood pressure; HDL-C=high-density lipoprotein-cholesterol; HOMA-IR-homeostatic model assessment-insulin resistance.

Table 4-8. Characteristics of clinical biomarkers according to patterns of drinking

	Class 1 None/light consumers n=297	**Class 2** Moderate beer, wine and spirit consumers n=1,673	**Class 3** Moderate-wine & heavy beer consumers n=250	**P_{value}**
Prevalence MetS	24 (8.1)	105 (6.3)	19 (7.6)	0.424
Continuous MetS	0.15 (0.78)	-0.02 (0.69)	-0.05 (0.72)	<0.001
Waist	84.4 (14.2)	82.8 (12.0)	87.8 (11.4)	<0.001
Triglycerides	1.1 (0.8)	1.3 (1.0)	1.1 (0.8)	<0.01
HDL-C	1.4 (0.3)	1.5 (0.3)	1.4 (0.3)	<0.001
Systolic BP	116 (13)	117 (13)	124 (12)	<0.001
Diastolic BP	72 (9)	72 (9)	74 (10)	<0.001
Glucose	4.9 (0.6)	5.0 (0.4)	5.1 (0.5)	<0.001
HOMA-IR	1.8 (1.4)	1.6 (1.1)	1.5 (1.3)	<0.01
Carotid IMT	0.55 (0.08)	0.56 (0.08)	0.57 (0.09)	<0.05

Data are shown as Number (Percentage) for categorical variables and as Mean (SD) for continuous variables.

MetS=metabolic syndrome; BP=blood pressure; HDL-C=high-density lipoprotein-cholesterol; HOMA-IR-homeostatic model assessment-insulin resistance.

Table 4-9. Multinomial regression on characteristics associated with pattern of alcohol consumption (N=2,220)

	Class 2 (n=1,673) Moderate beer, wine and spirit consumers						Class 3 (n=250) Moderate-wine & heavy beer consumers					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
	PR	(95%CIs)	P_{value}	PR	(95%CIs)	P_{value}	PR	(95%CIs)	P_{value}	PR	(95%CIs)	P_{value}
SES												
Quartiles 1	Ref			Ref			Ref			Ref		
Quartiles 2	0.50	(0.33, 0.77)	<0.05	0.07	(0.03, 0.19)	<0.001	0.92	(0.84, 0.99)	<0.05	0.95	(0.87, 1.04)	0.254
Quartiles 3	0.26	(0.15, 0.47)	<0.001	0.01	(0.00, 0.03)	<0.001	0.97	(0.90, 1.05)	0.434	0.98	(0.90, 1.07)	0.640
Quartiles 4	0.15	(0.06, 0.37)	<0.001	0.01	(0.00, 0.01)	<0.001	0.80	(0.69, 0.93)	<0.05	0.77	(0.65, 0.92)	<0.01
Occupation												
Professionals	Ref			Ref			Ref			Ref		
White collar	0.65	(0.39, 1.08)	0.098	0.20	(0.05, 0.72)	<0.05	0.95	(0.87, 1.04)	0.274	0.99	(0.88, 1.11)	0.852
Blue collar	1.79	(1.09, 2.94)	<0.05	0.17	(0.05, 0.65)	<0.01	0.72	(0.63, 0.81)	<0.001	0.72	(0.63, 0.83)	<0.001
Unemployed	0.54	(0.27, 1.09)	0.087	0.18	(0.06, 0.53)	<0.01	0.77	(0.68, 0.88)	<0.001	0.76	(0.67, 0.87)	<0.001
Marital status												

	Class 2 (n=1,673) Moderate beer, wine and spirit consumers						Class 3 (n=250) Moderate-wine & heavy beer consumers					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
Married/ de facto	Ref			Ref			Ref			Ref		
Single	0.97	(0.65, 1.46)	0.896	0.17	(0.07, 0.42)	<0.001	0.97	(0.91, 1.04)	0.436	0.91	(0.83, 1.00)	0.058
Divorced/ Separated	0.13	(0.02, 0.81)	<0.05	0.03	(0.01, 0.22)	<0.01	0.96	(0.85, 1.09)	0.557	0.93	(0.81, 1.07)	0.317
Total PA	1.00	(1.00, 1.00)	<0.01	1.00	(1.00, 1.00)	<0.001	1.00	(1.00, 1.00)	0.054	1.00	(1.00, 1.00)	<0.01
PWC_{170}	1.00	(1.00, 1.00)	0.307	1.00	(0.99, 1.01)	0.887	1.00	(1.00, 1.00)	0.073	1.00	(1.00, 1.00)	<0.05
DGI excluding alcohol	0.97	(0.96, 0.98)	<0.001	0.95	(0.94, 0.97)	<0.001	1.00	(1.00, 1.00)	<0.001	1.00	(1.00, 1.01)	<0.001
Physical HRQoL	1.02	(0.98, 1.05)	0.357	0.98	(0.96, 1.01)	0.229	1.01	(1.00, 1.01)	<0.05	1.01	(1.00, 1.02)	<0.01
Mental HRQoL	1.02	(0.99, 1.05)	0.218	0.92	(0.89, 0.96)	<0.001	1.00	(1.00, 1.00)	0.954	1.00	(1.00, 1.01)	0.098
Smoking	1.15	(0.75, 1.76)	0.534	2.35	(1.04, 5.31)	<0.05	1.50	(1.32, 1.68)	<0.001	1.59	(1.38, 1.83)	<0.001
Depression/ anxiety	1.38	(0.68, 2.80)	0.367	1.31	(0.63, 2.74)	0.474	1.01	(0.89, 1.14)	0.913	1.11	(1.00, 1.24)	0.051

Adjusted for age, sex and education level.

SES=socioeconomic status; PA=physical activity; PWC_{170}= physical work capacity; DGI=Dietary Guideline Index; HRQoL=health-related quality of life.

Multinomial regression models on characteristics associated with patterns of alcohol consumption were shown in Appendix Table 4-9. Those in the pattern of 'moderate beer, wine and spirit' consumers lived in higher socio-economic postcodes, had professional or managerial occupations, were more likely to be married, and more likely to be current smokers in adulthood. Similar results were seen in those who in the pattern of 'moderate-wine & heavy beer' consumers. These findings remained significant after adjusting for age, sex and educational level (Appendix Table 4-9).

Table 4-10. Multivariable linear regression analysis of the association between patterns of alcohol consumption and cardio-metabolic biomarkers (N=2,220)

Outcome	Exposure	Unadjusted		Adjusted	
	Drinking patterns	β (95% CI)	P_{value}	β (95% CI)	P_{value}
HOMA-IR	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	-0.15 (-0.28, -0.02)	<0.05	-0.01 (-0.17, 0.14)	0.897
	Moderate-wine & heavy beer consumers	-0.26 (-0.42, -0.10)	<0.01	-0.13 (-0.34, 0.08)	0.233
Carotid-IMT	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.01 (0.001, 0.02)	<0.05	0.02 (-0.03, 0.07)	0.398
	Moderate-wine & heavy beer consumers	0.02 (0.01, 0.03)	<0.05	-0.01 (-0.08, 0.06)	0.788
Continuous MetS score	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	-0.20 (-0.31, -0.10)	<0.001	-0.09 (-0.23, 0.04)	0.172
	Moderate-wine & heavy beer consumers	-0.22 (-0.36, -0.08)	<0.01	-0.14 (-0.33, 0.05)	0.142
Waist circumference	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	-2.12 (-3.83, -0.41)	<0.05	-1.07 (-3.28, 1.15)	0.345
	Moderate-wine & heavy beer consumers	3.10 (0.92, 5.28)	<0.01	-1.03 (-3.57, 1.51)	0.425
Triglycerides	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.01 (-0.07, 0.07)	0.941	-0.02 (-0.11, 0.06)	0.592

Outcome	Exposure	Unadjusted		Adjusted	
	Drinking patterns	β (95% CI)	P_{value}	β (95% CI)	P_{value}
	Moderate-wine & heavy beer consumers	0.13 (0.03, 0.24)	<0.01	-0.01 (-0.11, 0.11)	0.999
HDL cholesterol	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.06 (0.02, 0.10)	<0.01	0.08 (0.02, 0.13)	<0.01
	Moderate-wine & heavy beer consumers	0.09 (0.04, 0.14)	<0.001	0.28 (0.19, 0.37)	<0.001
Systolic BP	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	1.31 (-0.42, 3.04)	0.138	0.19 (-1.70, 2.07)	0.846
	Moderate-wine & heavy beer consumers	7.40 (5.15, 9.65)	<0.001	1.09 (-1.39, 3.57)	0.388
Diastolic BP	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	-0.74 (-1.96, 0.49)	0.240	-1.45 (-2.99, 0.10)	0.067
	Moderate-wine & heavy beer consumers	1.79 (0.03, 3.54)	<0.05	-0.36 (-2.67, 1.95)	0.759
Glucose	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.07 (0.01, 0.13)	<0.05	0.08 (0.01, 0.16)	<0.05
	Moderate-wine & heavy beer consumers	0.25 (0.18, 0.33)	<0.001	0.12 (0.02, 0.22)	<0.05

β =regression coefficient; CI=confidence interval. Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

Table 4-11. Multivariable regression analysis of the association between patterns of alcohol consumption and prevalence of cardio-metabolic abnormalities (N=2,220)

Outcome	Exposure	Unadjusted		Adjusted	
	Drinking patterns	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
Elevated HOMA	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.45 (0.31, 0.65)	<0.001	0.79 (0.44, 1.42)	0.430
	Moderate-wine & heavy beer consumers	0.41 (0.23, 0.72)	<0.01	0.74 (0.30, 1.83)	0.510
Elevated Carotid IMT	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.86 (0.55, 1.34)	0.506	1.12 (0.53, 2.36)	0.772
	Moderate-wine & heavy beer consumers	0.87 (0.45, 1.66)	0.663	1.00 (0.35, 2.87)	0.995
MetS	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.87 (0.53, 1.42)	0.577	1.36 (0.62, 2.98)	0.449
	Moderate-wine & heavy beer consumers	1.12 (0.58, 2.18)	0.738	1.71 (0.59, 4.90)	0.321
Central Obesity	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.42 (0.30, 0.58)	<0.001	0.57 (0.34, 0.94)	<0.05
	Moderate-wine & heavy beer consumers	0.43 (0.26, 0.72)	<0.001	0.70 (0.31, 1.59)	0.388
High triglycerides	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.79 (0.56, 1.12)	0.188	1.51 (0.75, 3.04)	0.247

Outcome	Exposure	Unadjusted		Adjusted	
	Drinking patterns	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
	Moderate-wine & heavy beer consumers	1.24 (0.79, 1.95)	0.349	1.80 (0.78, 4.19)	0.170
Low HDL-C	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.72 (0.49, 1.05)	0.091	0.68 (0.36, 1.29)	0.240
	Moderate-wine & heavy beer consumers	0.42 (0.23, 0.79)	<0.01	0.27 (0.10, 0.71)	<0.01
High blood pressure	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.64 (0.38, 1.06)	0.085	0.68 (0.31, 1.52)	0.350
	Moderate-wine & heavy beer consumers	1.31 (0.70, 2.42)	0.398	1.10 (0.41, 2.97)	0.851
High fasting glucose	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	1.33 (0.85, 2.08)	0.207	1.52 (0.75, 3.06)	0.246
	Moderate-wine & heavy beer consumers	2.52 (1.47, 4.31)	<0.01	1.49 (0.66, 3.39)	0.338

PR=prevalence ratio; CI=confidence interval. Adjusted for age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

Table 4-12. Multivariable linear regression analysis of the association between quantities of alcohol consumption and cardio-metabolic biomarkers (N=2,220)

Outcome	Exposure	Unadjusted		Adjusted	
	Drinking patterns	β (95% CI)	P_{value}	β (95% CI)	P_{value}
HOMA-IR	0g	0.11 (-0.03, 0.24)	0.115	-0.03 (-0.19, 0.13)	0.744
	>0-10g	Reference		Reference	
	>10-20g	-0.14 (-0.23, -0.05)	<0.01	-0.12 (-0.24, 0.01)	0.051
	>20-30g	-0.10 (-0.25, 0.05)	0.174	-0.01 (-0.24, 0.22)	0.923
	>30g	-0.25 (-0.40, -0.10)	<0.01	-0.25 (-0.45, -0.06)	<0.05
Carotid-IMT	0g	-0.01 (-0.02, -0.001)	<0.05	-0.03 (-0.07, 0.02)	0.296
	>0-10g	Reference		Reference	
	>10-20g	0.001 (-0.01, 0.01)	0.908	-0.03 (-0.07, 0.01)	0.061
	>20-30g	0.001 (-0.02, 0.02)	0.923	-0.03 (-0.08, 0.03)	0.370
	>30g	0.01 (-0.01, 0.02)	0.515	-0.03 (-0.10, 0.04)	0.404
Continuous MetS score	0g	0.16 (0.05, 0.27)	<0.01	0.07 (-0.07, 0.21)	0.337
	>0-10g	Reference		Reference	
	>10-20g	-0.12 (-0.20, -0.04)	<0.01	-0.09 (-0.20, 0.02)	0.105
	>20-30g	-0.14 (-0.28, 0.01)	0.055	-0.09 (-0.29, 0.12)	0.423
	>30g	-0.05 (-0.19, 0.10)	0.537	-0.07 (-0.26, 0.13)	0.506
Waist circumference	0g	1.88 (0.41, 3.36)	<0.05	1.04 (-0.98, 3.05)	0.313
	>0-10g	Reference		Reference	
	>10-20g	-0.79 (-2.00, 0.42)	0.200	-0.97 (-2.33, 0.38)	0.159
	>20-30g	-0.63 (-2.76, 1.49)	0.558	-0.02 (-2.33, 2.28)	0.983
	>30g	-0.80 (-2.89, 1.29)	0.454	-1.58 (-3.86, 0.71)	0.177
Triglycerides	0g	-0.01 (-0.08, 0.06)	0.726	0.02 (-0.07, 0.11)	0.714
	>0-10g	Reference		Reference	

Outcome	Exposure	Unadjusted		Adjusted	
	Drinking patterns	β (95% CI)	P_{value}	β (95% CI)	P_{value}
	>10-20g	0.03 (-0.03, 0.09)	0.277	0.01 (-0.06, 0.08)	0.734
	>20-30g	0.03 (-0.07, 0.14)	0.531	-0.03 (-0.15, 0.09)	0.659
	>30g	0.06 (-0.04, 0.17)	0.238	0.01 (-0.11, 0.12)	0.938
HDL-C	0g	-0.04 (-0.08, 0.01)	0.062	-0.05 (-0.11, 0.01)	0.060
	>0-10g	Reference		Reference	
	>10-20g	0.04 (0.01, 0.08)	<0.05	0.11 (0.06, 0.16)	<0.001
	>20-30g	0.13 (0.06, 0.19)	<0.001	0.23 (0.15, 0.31)	<0.001
	>30g	0.11 (0.05, 0.17)	<0.001	0.22 (0.11, 0.33)	<0.001
Systolic blood pressure	0g	-0.88 (-2.67, 0.91)	0.333	0.08 (-1.85, 2.01)	0.939
	>0-10g	Reference		Reference	
	>10-20g	2.35 (0.98, 3.72)	<0.01	0.26 (-1.22, 1.73)	0.735
	>20-30g	3.71 (1.46, 5.99)	<0.01	0.45 (-1.84, 2.75)	0.699
	>30g	6.44 (3.88, 9.01)	<0.001	3.84 (0.89, 6.78)	<0.05
Diastolic blood pressure	0g	0.90 (-0.37, 2.17)	0.166	1.68 (0.10, 3.27)	<0.05
	>0-10g	Reference		Reference	
	>10-20g	0.43 (-0.56, 1.43)	0.394	0.28 (-0.99, 1.54)	0.668
	>20-30g	2.26 (0.46, 4.05)	<0.05	2.25 (-0.31, 4.80)	0.085
	>30g	3.79 (1.73, 5.85)	<0.001	2.89 (0.27, 5.51)	<0.05
Glucose	0g	-0.06 (-0.13, -0.01)	<0.05	-0.08 (-0.16, -0.01)	<0.05
	>0-10g	Reference		Reference	
	>10-20g	0.06 (0.01, 0.10)	<0.05	-0.01 (-0.06, 0.06)	0.934
	>20-30g	0.11 (0.03, 0.19)	<0.01	0.04 (-0.05, 0.14)	0.354
	>30g	0.14 (0.05, 0.24)	<0.01	0.06 (-0.03, 0.16)	0.182

β =regression coefficient; CI=confidence interval. Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

Table 4-13. Multivariable regression analysis of the association between quantities of alcohol consumption and prevalence of cardio-metabolic abnormalities (N=2,220)

Outcome	Exposure	Unadjusted		Adjusted	
	Drinking patterns	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
Prevalence of elevated HOMA	0g	1.85 (1.27, 2.69)	<0.01	1.09 (0.60, 1.98)	0.767
	>0-10g	Reference		Reference	
	>10-20g	0.44 (0.28, 0.68)	<0.001	0.38 (0.20, 0.73)	<0.01
	>20-30g	0.72 (0.33, 1.60)	0.422	1.06 (0.36, 3.13)	0.913
	>30g	0.46 (0.21, 1.03)	0.059	0.43 (0.14, 1.33)	0.144
Prevalence of elevated Carotid IMT	0g	1.13 (0.72, 1.79)	0.592	0.88 (0.41, 1.86)	0.734
	>0-10g	Reference		Reference	
	>10-20g	0.95 (0.62, 1.45)	0.813	0.81 (0.47, 1.39)	0.438
	>20-30g	0.51 (0.19, 1.34)	0.169	0.51 (0.17, 1.56)	0.241
	>30g	1.01 (0.09, 0.14)	0.989	1.35 (0.57, 3.18)	0.496
Prevalence of MetS	0g	1.05 (0.63, 1.72)	0.861	0.69 (0.31, 1.53)	0.366
	>0-10g	Reference		Reference	
	>10-20g	0.77 (0.48, 1.23)	0.279	0.73 (0.37, 1.44)	0.364
	>20-30g	0.64 (0.21, 1.96)	0.433	0.87 (0.17, 4.45)	0.868
	>30g	1.00 (0.48, 2.08)	0.993	1.08 (0.43, 2.71)	0.862
Central Obesity	0g	2.10 (1.49, 2.97)	<0.001	1.59 (0.95, 2.67)	0.079
	>0-10g	Reference		Reference	
	>10-20g	0.66 (0.46, 0.96)	<0.05	0.84 (0.47, 1.48)	0.537

Outcome	Exposure	Unadjusted		Adjusted	
	Drinking patterns	PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
	>20-30g	0.71 (0.33, 1.52)	0.382	0.95 (0.26, 3.48)	0.934
	>30g	0.81 (0.44, 1.51)	0.510	0.94 (0.42, 2.11)	0.876
High triglycerides	0g	1.22 (0.84, 1.75)	0.295	0.60 (0.29, 1.25)	0.176
	>0-10g	Reference		Reference	
	>10-20g	1.08 (0.80, 1.47)	0.614	1.01 (0.64, 1.59)	0.973
	>20-30g	1.18 (0.66, 2.11)	0.568	1.26 (0.54, 2.92)	0.596
	>30g	1.31 (0.80, 2.14)	0.285	1.05 (0.51, 2.18)	0.892
Low HDL-C	0g	1.26 (0.85, 1.86)	0.250	1.40 (0.74, 2.65)	0.300
	>0-10g	Reference		Reference	
	>10-20g	0.66 (0.45, 0.97)	<0.05	0.78 (0.45, 1.34)	0.362
	>20-30g	0.23 (0.09, 0.78)	<0.05	0.11 (0.02, 0.53)	<0.01
	>30g	0.46 (0.20, 1.02)	0.057	0.38 (0.12, 1.24)	0.110
High blood pressure	0g	1.73 (1.01, 2.94)	<0.05	1.74 (0.75, 4.00)	0.195
	>0-10g	Reference		Reference	
	>10-20g	1.34 (0.88, 2.05)	0.172	1.53 (0.82, 2.84)	0.182
	>20-30g	0.82 (0.34, 1.95)	0.647	1.01 (0.28, 3.52)	0.999
	>30g	3.72 (2.15, 6.40)	<0.001	3.66 (1.60, 8.37)	<0.01
High fasting glucose	0g	0.78 (0.49, 1.24)	0.290	0.65 (0.32, 1.32)	0.234
	>0-10g	Reference		Reference	
	>10-20g	1.33 (0.93, 1.90)	0.114	0.91 (0.56, 1.49)	0.713
	>20-30g	1.13 (0.59, 2.17)	0.706	0.71 (0.29, 1.75)	0.463
	>30g	1.65 (0.95, 2.85)	0.075	0.95 (0.46, 1.94)	0.882

PR=prevalence ratio; CI=confidence interval. Adjusted for age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

Table 4-14. Model performance and comparisons of pattern of alcohol consumption with total alcohol consumed in predicting high carotid IMT & high HOMA-IR

Outcome	N	Exposure	AUC (95% CI)	Deviance
Elevated HOMA-IR	1,257	Patterns	0.62 (0.57, 0.67)	5,331.4
		Quantity	0.65 (0.60, 0.70)	5,295.6
Elevated Carotid-IMT	1,116	Patterns	0.61 (0.56, 0.66)	5,642.5
		Quantity	0.61 (0.56, 0.66)	5,644.0

AUC= area under the curve. Adjusted for age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

Table 4-15. Sensitivity analysis of the association alcohol consumption by patterns and total amounts per day consumed and HOMA-IR and carotid IMT after excluding participants with alcohol use disorder

Outcome	Exposure	All participants		Excluding those with an alcohol use disorder	
		β (95% CI)	P_{value}	β (95% CI)	P_{value}
HOMA	Drinking patterns				
	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	-0.01 (-0.17, 0.14)	0.897	-0.03 (-0.23, 0.16)	0.708
	Moderate-wine & heavy beer consumers	-0.13 (-0.34, 0.08)	0.233	-0.20 (-0.55, 0.05)	0.097
	Amounts per day				
	0g	-0.03 (-0.19, 0.13)	0.744	-0.01 (-0.20, 0.19)	0.924
	>0-10g	Reference		Reference	
	>10-20g	-0.12 (-0.24, 0.01)	0.051	-0.17 (-0.33, -0.01)	0.05
	>20-30g	-0.01 (-0.24, 0.22)	0.923	-0.02 (-0.40, 0.17)	0.387
	>30g	-0.25 (-0.45, -0.06)	<0.05	-0.30 (-0.79, -0.10)	<0.05
Carotid IMT	Drinking patterns				
	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	0.02 (-0.03, 0.07)	0.398	0.01 (-0.01, 0.03)	0.128
	Moderate-wine & heavy beer consumers	-0.01 (-0.08, 0.06)	0.788	-0.01 (-0.02, 0.04)	0.308
	Amounts per day				
	0g	-0.03 (-0.07, 0.02)	0.296	-0.02 (-0.03, 0.01)	0.094
	>0-10g	Reference		Reference	

>10-20g	-0.03 (-0.07, 0.01)	0.061	-0.02 (-0.03, 0.01)	0.333
>20-30g	-0.03 (-0.08, 0.03)	0.370	-0.02 (-0.03, 0.02)	0.528
>30g	-0.03 (-0.10, 0.04)	0.404	0.01 (-0.03, 0.03)	0.717

β =regression coefficient; CI=confidence interval. Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

Table 4-16. Sensitivity analysis of the association alcohol consumption by patterns and total amounts per day consumed and prevalence of elevated HOMA and prevalence of elevated carotid IMT after excluding participants with alcohol use disorder

Outcome	Exposure	All participants		Excluding those with an alcohol use disorder	
		PR (95% CI)	P_{value}	PR (95% CI)	P_{value}
Prevalence of elevated HOMA	Drinking patterns				
	None/light consumers	Reference		Reference	
	Moderate beer, wine and spirit consumers	1.12 (0.53, 2.36)	0.772	1.10 (0.30, 1.33)	0.214
	Moderate-wine & heavy beer consumers	1.00 (0.35, 2.87)	0.995	0.90 (0.53, 1.27)	0.373
	Amounts per day				
	0g	1.09 (0.60, 1.98)	0.767	1.10 (0.71, 1.70)	0.671
	>0-10g	Reference		Reference	
	>10-20g	0.38 (0.20, 0.73)	<0.01	0.44 (0.25, 0.77)	<0.01
	>20-30g	1.06 (0.36, 3.13)	0.913	0.66 (0.27, 1.57)	0.342
	>30g	0.43 (0.14, 1.33)	0.144	0.43 (0.16, 1.15)	0.093
	Drinking patterns				
	None/light consumers	Reference		Reference	

Prevalence of elevated Carotid IMT	Moderate beer, wine and spirit consumers	1.36 (0.62, 2.98)	0.449	1.18 (0.50, 2.78)	0.724
	Moderate-wine & heavy beer consumers	1.71 (0.59, 4.90)	0.321	1.45 (0.83, 2.52)	0.192
	Amounts per day				
	0g	0.81 (0.47, 1.39)	0.438	0.71 (0.41, 1.21)	0.208
	>0-10g	Reference		Reference	
	>10-20g	0.51 (0.17, 1.56)	0.241	0.73 (0.46, 1.15)	0.178
	>20-30g	1.35 (0.57, 3.18)	0.496	1.12 (0.60, 2.09)	0.712
	>30g	0.88 (0.41, 1.86)	0.734	0.60 (0.23, 1.58)	0.297

PR=prevalence ratio; CI=confidence interval. Adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking status, dietary intakes, physical activity, cardiorespiratory fitness, depression and anxiety

Chapter 5

The metabolomics signatures of alcohol consumption in young adults

Submitted to

International Journal of Cardiology 2018

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5 Chapter 5. The metabolomics signatures of alcohol consumption in young adults

5.1. Introduction

Recent studies have contradicted the previous evidence of benefits of low to moderate consumption of alcohol for reducing cardiovascular disease risk [117]. The emerging technology of metabolomic analysis provides a snapshot of systemic metabolism that may increase understanding of the association between alcohol consumption and cardio-metabolic health, particularly the contradictory effects of reducing risk of myocardial infarction but increasing risk of a host of other cardiovascular diseases [117].

One previous study examined metabolites associated with alcohol consumption, which revealed that higher alcohol consumption was associated with higher HDL-C and monounsaturated FA, but lower omega-6 FA, glutamine, citrate and lipoprotein particle size in three cohorts using a nuclear magnetic resonance (NMR) platform [145]. Most of these biomarkers have been shown to be associated with CVD events or risk [242]. Replication of results in other cohorts is important in this emerging field to understand generalisability. Further, it is not known whether the type of alcoholic beverage consumed influences relationships and potentially important covariates such as diet, CRF and mental health have not been examined.

We aimed to (1) replicate previous findings between alcohol consumption and metabolic profiles; (2) examine the association of different types of alcoholic beverages (beer and wine) with metabolites and (3) consider covariates not previously examined (e.g. diet, CRF and mental health) in associations between metabolic profiles and alcohol consumption.

5.2. Methods

5.2.1. Participants

Participants were from the 2004–2006 CDAH study, a 20-year follow-up study of the ASHFS that was conducted in 1985 [243]. In total, a representative sample of 8,498 Australian school children (51% male, aged 7 to 15 years) from 109 schools participated in the ASHFS. Of the original 8,498 participants, 5,170 (60.8%) enrolled in the CDAH study and 2,410 (28.4%) attended 1 of 34 study clinics held across Australia from 2004 to 2006 when aged between 26 and 36 years [243]. Of these participants, 74% had data available for alcohol consumption completed by questionnaires, gave a fasting blood sample, and had their metabolomics profile measured by a serum NMR platform. A detailed description of the cohort has been published elsewhere [204]. The flow of participants from baseline to follow-up is described in Figure 5-1. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee. All participants gave informed written consent.

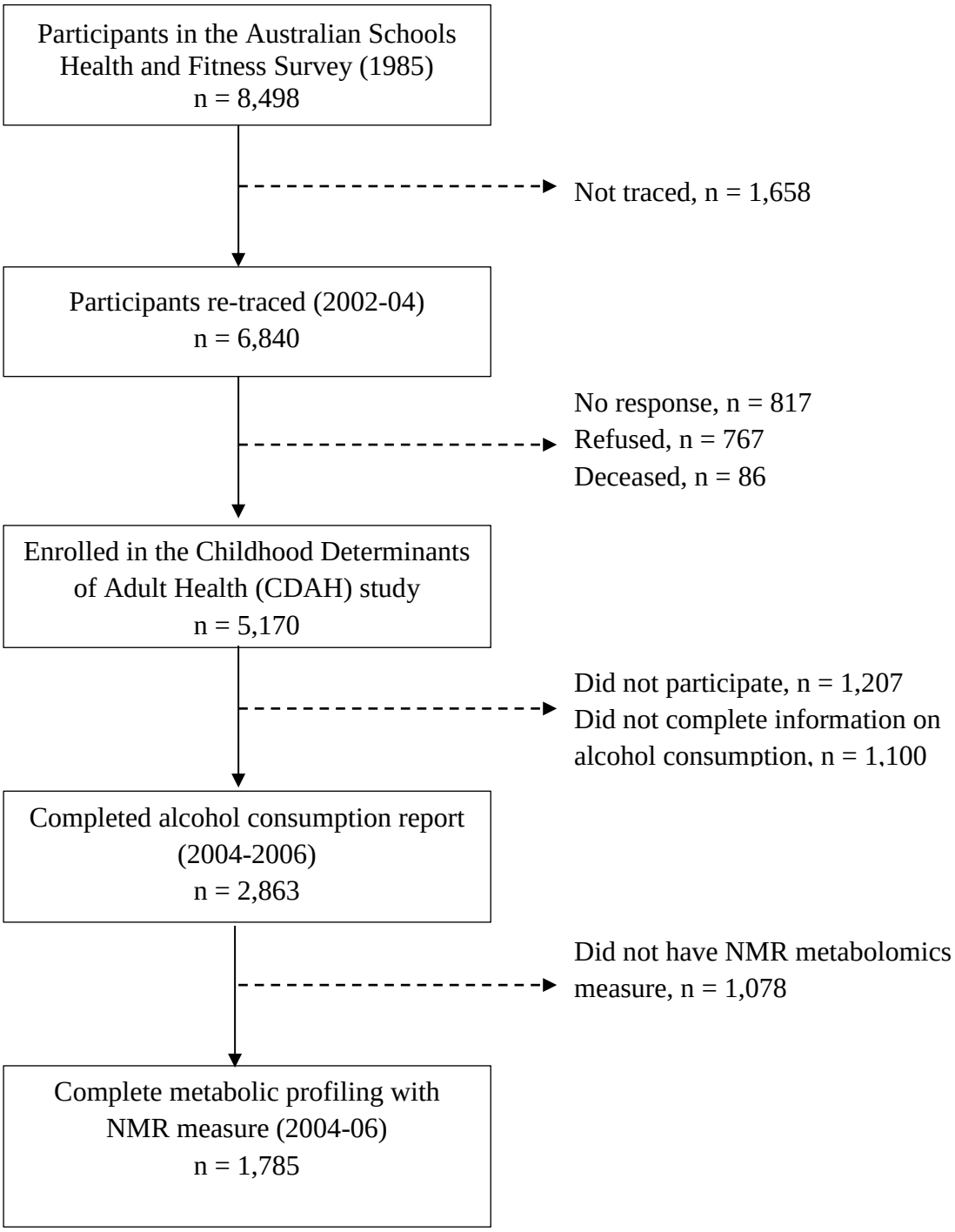


Figure 5-1. Flow chart of alcohol consumption status and metabolite outcomes during follow-up periods

5.2.2. Measurements

5.2.2.1. Alcohol consumption

Each participant reported his or her frequency of intake (options: never or <1/month, 1–3 times/month, once/week, 2–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–5 times/day, and >6 times/day) of 10 alcoholic beverages (light, medium or full strength beer; red, white and sparkling wine; wine cooler; spirits/liqueurs; spirit-based mixed drinks; sherry/port and other) over the last 12 months in a FFQ. We assumed that one standard drink (10 g of alcohol) was consumed on each drinking occasion. We estimated the alcohol consumed per day for each beverage type by multiplying the frequency of drinking by the estimated grams of alcohol for each beverage type: beer (sum of light beer, medium strength beer and full-strength beer) and wine (sum of red and white wine). Spirits were infrequently consumed; therefore, they were not examined in the analyses. Total alcohol consumed per week and per day was the sum of all 10 types of beverages [174].

5.2.2.2. Metabolomics

Fasting blood samples were stored at −80ºC for 11–13 years. The computational medicine metabolomic platform used high-throughput serum NMR spectroscopy to quantify 223 key metabolic markers [244]. As per previous studies, we focused on 73 metabolic measures covering major biological pathways [244].

5.2.2.3. Covariates

Full details of the measurement of covariates are provided in the appendix. In brief, covariates were age, sex, SES as quartile based on area of residence (high, medium-high, medium-low or low), region of residence (major city/urban/rural areas), education level (university, vocational or secondary school only), occupation (professional/manager, white collar, blue collar or not in labour force), marital status (married or living as married vs other), smoking status (never, former or current), total physical activity (minutes per week, mins/week), CRF (PWC_{170} uncorrelated with lean body mass) [220], diet quality (DGI) [222] and depression and anxiety diagnosis in the previous 12 months (CIDI) [205].

5.2.3. Statistical analysis

We used multivariable linear regression models to examine associations between alcohol consumption as the explanatory variable and each metabolic measure as the outcome (β coefficients and 95% CIs). Alcohol consumption was examined as 1) total alcohol consumption (grams per week) and 2) by beverage type (beer or wine). All metabolic variables were scaled to standard deviation units and those with skewed distributions were log transformed before analysis. Results are presented graphically with numerical results also provided in the appendix.

The continuous shape of the significant linear metabolic pathways associated with alcohol consumption were examined graphically using local quadratic regression fitting, with each smoothing function segment evaluated at 25 points through the range of alcohol intake. More complex shapes were further examined using polynomial regression models to obtain the standard deviation changes of metabolite measures with log transformation when required.

Potential covariates were included in the models in accordance with purposeful model building procedures [208]. Models are presented adjusted for sex, age (model 1); model 1 plus region of residence, SES, educational level, occupation, marital status, smoking, dietary intakes, physical activity, CRF and depression and/or anxiety (model 2).

The following sensitivity analyses were performed: (1) using total alcohol consumption in grams per day instead of grams per week, and (2) to test whether drinking alcohol the day before the blood test influenced the results.

We adjusted for multiple statistical testing using the number of principal components that explained over 99% variance of the metabolomics data to determine the independent number of tests [145]. As 36 principal components were identified, the corrected significance threshold was $P \leq 0.002$ (two-tailed). Analysis was performed with the RStudio 1.0.136 software program using the MASS, metafor, AER, RColorBrewer, ggplot2 (R Core Team, 2016) and Stata 12.0 packages.

5.3. Results

5.3.1. Characteristics of study population

The study population consisted of 1,785 participants in the cohort who had complete data on alcohol consumption and metabolomic measures (Table 5-1). Participants with and without metabolomics data had similar characteristics (Table 5-1).

Table 5-1. Characteristics of the study population

Characteristic	Participants with metabolomics data (N=1,785)	Participants without metabolomics data (N=1,078)	P_{value}
Number of participants (men/women)	811/974	465/613	0.231
Age (years)	31.3 (2.6)	32.0 (2.6)	<0.001
Body mass index (kg/m^2)	25.6 (4.8)	25.6 (5.0)	0.953
Systolic blood pressure (mmHg)	118 (12)	119 (13)	<0.05
Total cholesterol (mmol/l)	4.9 (1.0)	5.0 (1.0)	<0.05
HDL cholesterol (mmol/l)	1.4 (0.3)	1.4 (0.3)	0.226
Triglycerides (mmol/l)	0.9 (0.6-1.3)	0.9 (0.6-1.4)	0.513
Plasma glucose (mmol/l)	5.0 (4.7-5.2)	5.0 (4.7-5.3)	0.507
Insulin (IU/l)	6.0 (4.3-8.6)	5.9 (4.2-8.2)	0.487
HOMA-IR	1.3 (0.9-1.9)	1.3 (0.9-1.9)	0.489
cMSy	-0.01 (0.7)	0.03 (0.7)	0.198
Smoking prevalence, n (%)	369 (22)	121 (22)	0.994
Total alcohol consumption (g/week)	41.0 (15.0-87.5)	36.8 (11.8-82.5)	0.480
Total alcohol consumption (g/day)	5.9 (2.1-12.5)	5.3 (1.7-11.8)	0.480
Total beer (g/day)	1.1 (0.0-4.5)	0.7 (0.0-4.3)	0.487
Total wine (g/day)	2.1 (0.0-4.3)	1.1 (0.0-4.3)	0.473
Total spirits (g/day)	0.7 (0.0-1.7)	0.7 (0.0-1.7)	0.485

Characteristic	Participants with metabolomics data (N=1,785)	Participants without metabolomics data (N=1,078)	P_{value}
Alcohol consumption status, n (%)			0.065
Non-drinkers (0 g/day)	246 (14)	187 (17)	
Light drinkers (>0-10 g/day)	974 (55)	563 (52)	
Moderate drinkers (>10-20 g/day)	386 (22)	209 (19)	
Heavy drinkers (>20-30 g/day)	88 (5)	55 (5)	
Very heavy drinkers (>30 g/day)	91 (5)	64 (6)	

Abbreviation: HDL, High-Density Lipoprotein; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance; cMSy, Continuous Metabolic Syndrome Risk Scores. Data are shown as mean (± standard deviation) or median (interquartile range) for normally distributed or skewed continuous variables, respectively; and number (percentage) for categorical variables.

5.3.2. Associations of alcohol with lipoprotein lipids

Alcohol consumption was associated with 23 out of 37 lipoprotein and lipid measures (see Figure 5-2, Appendix Table 5-2 and Table 5-3 for numerical results). In the fully adjusted model, alcohol consumption per 100 g/week was strongly associated with higher lipid concentrations for all HDL subclasses, particularly for the medium-sized and large HDL particles. Concurrently, the HDL-C, apolipoprotein A-1, phosphoglycerides and phosphatidylcholine concentrations were robustly elevated in relation to higher alcohol consumption. In contrast, higher alcohol consumption was strongly associated with smaller LDL particle size, lower levels of apolipoprotein B, lower levels of remnant cholesterol, intermediate (IDL) cholesterol and VLDL cholesterol concentrations. Adjustment for demographic factors (model 1) and other health behaviours (model 2) mostly increased the magnitude of the associations compared to the unadjusted model (Appendix Table 5-4). Similar results were observed when alcohol was examined as 10 g of alcohol per day instead of the weekly basis (Appendix Figure 5-8).

In the fully adjusted model, beer and wine consumption were positively associated with all HDL concentrations including large-, medium- and small-sized particles, HDL particle size, apolipoprotein A-1, HDL-C, phosphatidylcholine, and phosphoglycerides concentration

while inversely associated with apolipoprotein B, remnant cholesterol and VLDL cholesterol. There was evidence that beer consumption was associated with larger increases in lipid concentrations in the large, medium and small HDL subclasses, HDL particle size, HDL-C, apolipoprotein A-1, phosphoglycerides and phosphatidylcholine concentrations compared to wine consumption or total alcohol consumption.

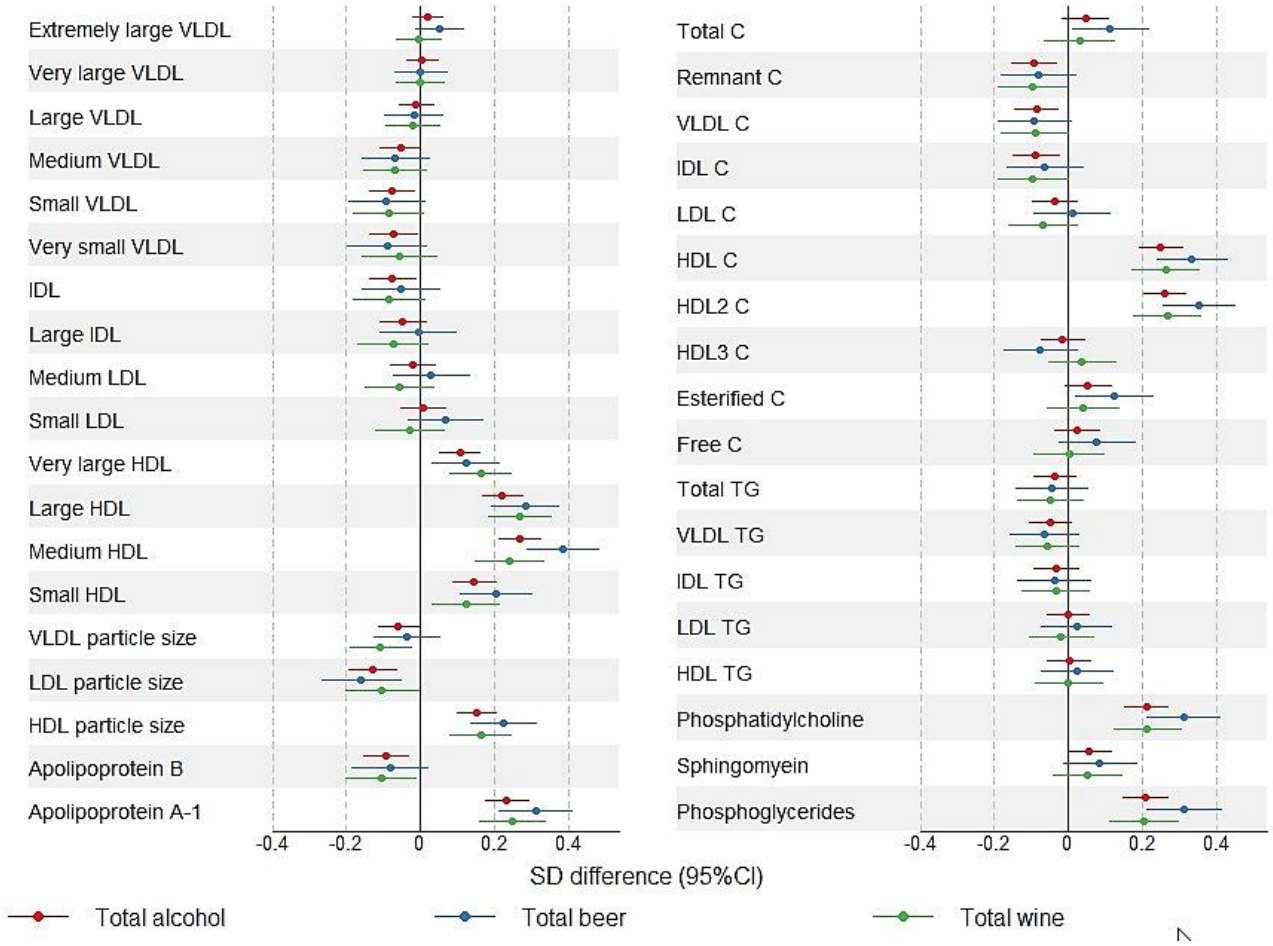


Figure 5-2. Cross-sectional associations between alcohol consumption as total alcohol, beer and wine consumed and lipoprotein lipid measures.

All association were adjusted for age, sex, region of residence, SES, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety. Error bars denote 95% confidence intervals. Differences in metabolite concentration are expressed as standard deviation difference (95% CIs) per 100 grams of alcohol per week. Association magnitudes in absolute concentration units are listed in Appendix Table 5-2 and continuous shapes of the metabolic associations with alcohol intake are shown in Appendix Figure 5-14 to Figure 5-16.

When further examining the shape of the associations, HDL-related, phosphoglycerides and apolipoprotein A-1 measures were mainly linear across the range of alcohol consumption. Inverse linear associations were observed in the measures of LDL particle size, apolipoprotein B, remnant cholesterol and IDL cholesterol (Appendix Figure 5-14 to Figure 5-16).

Non-linear associations were observed between alcohol consumption with higher lipid concentrations in the large and small HDL subclasses, larger HDL particle size, higher HDL-C, higher apolipoprotein A-1, and higher phosphoglycerides and phosphatidylcholine concentrations (Appendix Table 5-3).

5.3.3. Associations of alcohol with fatty acids

Alcohol consumption was associated with 12 out of 16 FA measures (see Figure 5-3, Appendix Table 5-2 and Table 5-3). Higher alcohol consumption was robustly associated with higher concentrations of total FA, saturated FA, monounsaturated fatty acids (MUFA), omega-3 FA and docosahexaenoic acid (DHA) in absolute concentrations, and higher proportions of saturated FA, omega-3 FA and DHA levels to total FA. In contrast, alcohol consumption was inversely associated with the omega-6 FA ratio, polyunsaturated fatty acids (PUFA) ratio and linoleic acid ratio to total FA. These results remained statistically significant after adjusting for potential covariates (Figure 5-3). Smoking, diet, physical activity and CRF (model 2) caused most of the changes in the associations (Appendix Table 5-4).

In the fully adjusted models, similar results were observed with beer and wine consumption and FA measures. There was evidence that beer consumption led to a larger increase in the magnitudes of associations among total FA, saturated FA, MUFA, PUFA, omega-6 FA, omega-3 FA, DHA and a larger decrease in associations of PUFA ratio, omega-6 FA ratio and linolenic acid ratio to total FA compared to wine consumption or total alcohol consumption.

Similar results were observed when the standard deviation differences of metabolite concentrations were compared per 10 g of alcohol per day instead of the weekly basis (Appendix Figure 5-9).

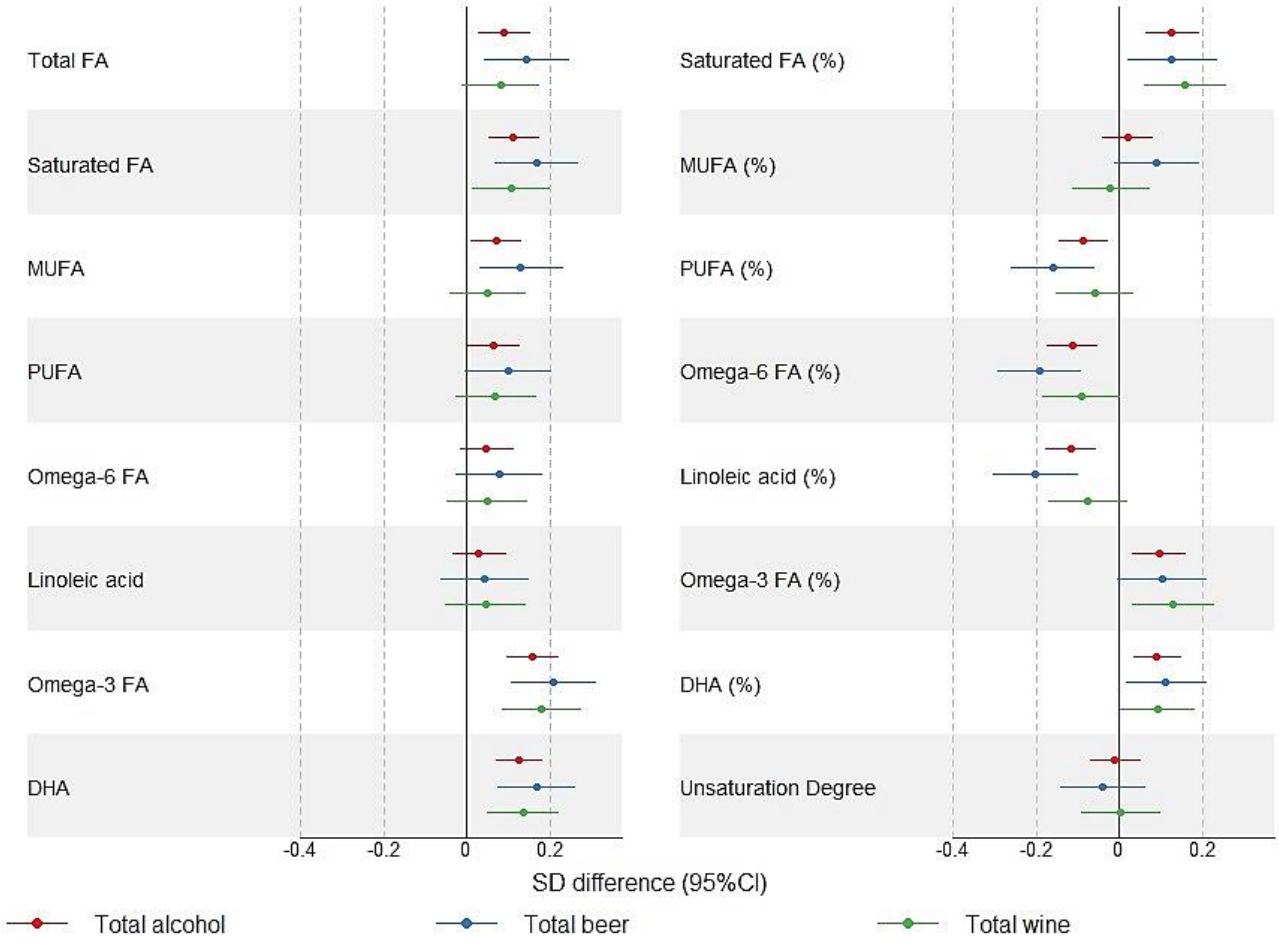


Figure 5-3. Cross-sectional associations between alcohol consumption as total alcohol, beer and wine consumed and fatty acids.

All association were adjusted for age, sex, region of residence, SES, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety. Error bars denote 95% confidence intervals. Differences in metabolite concentration are expressed as standard deviation difference (95% CIs) per 100 grams of alcohol per week. Association magnitudes in absolute concentration units are listed in Appendix Table 5-2 and continuous shapes of the metabolic associations with alcohol intake are shown in Appendix Figure 5-17.

When examining the shapes of these associations, most were linear across the range of alcohol consumption. Inverse linear associations were observed in the measures of omega-6 FA ratio, linoleic acid ratio and PUFA to total FA. In contrast, positive linear associations were observed in the measures of omega-3 FA and DHA, or largely positive in measures of total FA, saturated FA, MUFA, PUFA, omega-6 FA concentrations, saturated FA and MUFA ratio to total FA where the slope modestly decreased in light alcohol consumption but increased across higher ranges of alcohol consumption (Figure 5-17).

5.3.4. Associations of alcohol with low-molecular-weight metabolites

Alcohol consumption was associated with 6 out of 20 low molecular weight metabolite measures (see Figure 5-4, Supplementary Table 5-2 and Table 5-3). The strongest associations between alcohol and low molecular weight metabolites were observed for glycine, isoleucine, valine, phenylalanine and citrate, which were all inversely associated with higher alcohol consumption (Figure 5-4). Demographic factors including sex, age and SES status (model 1) and smoking, diet, physical activity and CRF (model 2) accounted for most of the significant changes in the magnitude of the associations compared to the unadjusted model (Appendix Table 5-4). While most of the small molecular metabolites were not strongly associated with alcohol consumption based on the linear models, subtle non-linear associations were evident for several measures, e.g. phenylalanine (Appendix Table 5-3 and Figure 5-18). Similar results were observed when the standard deviation differences of metabolite concentration were compared per 10 g of alcohol per day instead of the weekly basis (Appendix Figure 5-10).

In the fully adjusted model, similar results were observed for both beer and wine consumption.

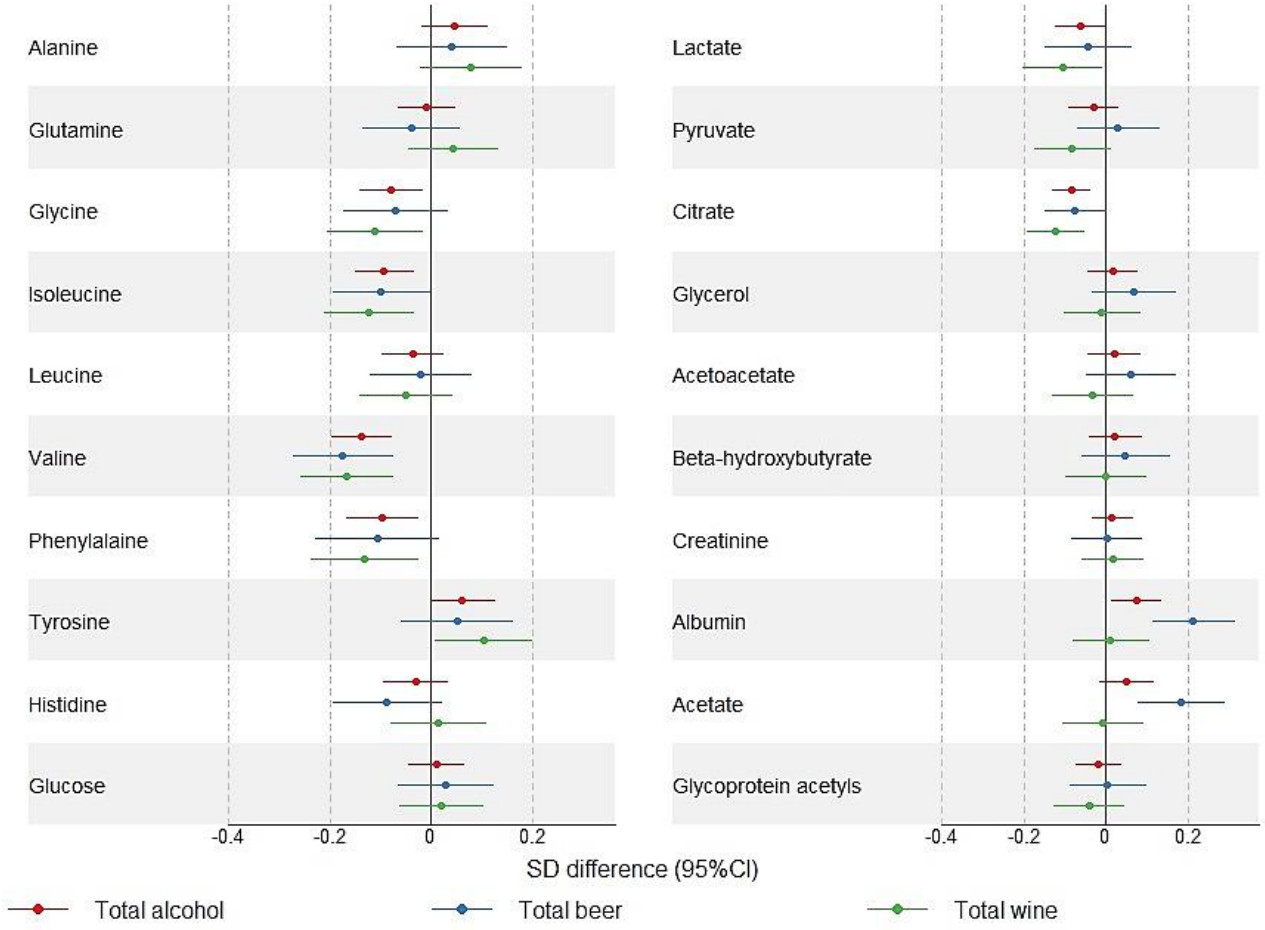


Figure 5-4. Cross-sectional associations between alcohol consumption as total alcohol, beer and wine consumed and low-molecular-weight metabolites.

All association were adjusted for age, sex, region of residence, SES, educational level, occupation, marital status, smoking, dietary intakes, physical activity, cardiorespiratory fitness, depression and/or anxiety. Error bars denote 95% confidence intervals. Differences in metabolite concentration are expressed as standard deviation difference (95% CIs) per 100 grams of alcohol per week. Association magnitudes in absolute concentration units are listed in Appendix Table 5-2 and continuous shapes of the metabolic associations with alcohol intake are shown in Appendix Figure 18 and Figure 19.

5.4. Discussion

The metabolomic signatures of this young adult cohort revealed diverse molecular processes related to alcohol consumption, comprising both favourable and unfavourable effects in relation to the risk of cardio-metabolic diseases. Our results were largely similar to the previous study [145] except for associations with some triglycerides, FA and several low molecular weight metabolites. We generally found limited differences in associations between types of beverages. Including diet and CRF fitness, but not mental health, appeared to influence the associations, suggesting that inadequate control for confounders might have led to a miss-estimation of the associations between alcohol consumption and some of these measures in previous studies.

5.4.1. Associations of alcohol with lipoprotein lipids

Our findings on the associations between alcohol consumption and lipid and lipoprotein measures were mostly consistent with the only other previous study on alcohol consumption and metabolomic profiling in young adults [145]. This included that alcohol consumption was positively associated with several lipid and lipoprotein measures related to lower cardiovascular risk, e.g. large and small HDL subclasses, HDL particle size, HDL-C and apolipoprotein A-1. Associations between alcohol consumption and phosphoglycerides, phosphatidylcholine and apolipoprotein A-1 were non-linear, with less positive effects at higher levels of alcohol consumption.

Consistent with the previous study [145], higher alcohol consumption was strongly associated with several lipid and lipoprotein measures (smaller LDL particle size, higher phosphoglycerides and phosphatidylcholine) related to greater cardiovascular risk.

Alcohol consumption was not associated with serum total triglycerides and triglycerides in HDL, which contrasts to the previous study [145]. Explanations for this include differences in the populations in the determinants of triglycerides (e.g. diet and body weight [245]); however, we adjusted for these and no associations were evident in the unadjusted analyses. This suggests that further examination is required to confirm the associations between alcohol consumption and triglycerides.

We found that beer and wine consumption had associations with lipids and lipoproteins that were similar to total alcohol consumption. There was some evidence that beer consumption was associated with larger increases in lipid concentrations in the large, medium and small HDL subclasses, HDL particle size, HDL-C, apolipoprotein A-1, phosphoglycerides and phosphatidylcholine concentrations than wine or total alcohol consumption. This might be influenced by demographic characteristics and health behaviours in people that drink beer because these factors accounted for large increases in the associations, suggesting negative confounding effects. These findings suggest that the common components of alcohol might affect lipids, noting a meta-analysis showing similar J-shaped associations between beer and wine consumption with cardiovascular events [246].

Adjusting for CRF and diet increased the magnitudes of the associations between alcohol and lipid concentrations in the large, medium and small HDL subclasses, HDL particle size, HDL-C, apolipoprotein A-1, phosphoglycerides and phosphatidylcholine concentrations. This highlights the close interaction between CRF, diet and alcohol consumption [75] that might explain some of the pathways to cardio-metabolic diseases through lipids and lipoproteins.

Numerous studies have indicated strong associations between higher alcohol consumption and elevated HDL-C, adiponectin and apolipoprotein A-1 levels [247, 248]. Alcohol might influence HDL-C via CETP activity [249], in combination with the increased transport rate of apolipoproteins [212] and reduced hepatic lipase activity [250]. In turn, HDL-C moves excess cholesterol molecules from peripheral cells to the liver [251]. Alcohol was associated with higher apolipoprotein A-1 concentration mainly due to the increase in the A-1 lipoprotein particle, which has been suggested to represent the antiatherogenic fraction of HDL [252]. The underlying mechanisms by which alcohol affects LDL particle size, phosphoglycerides and phosphatidylcholine are not well-established. However, there is evidence linking lower LDL particle size and plasma triglyceride-rich lipoprotein particles, such as phosphoglycerides and phosphatidylcholine [253], to the progression of CHD [254]. These conflicting effects of alcohol consumption on lipids and lipoproteins coupled with recent findings on metabolic markers differentially predicting myocardial infarction and stroke [255] might explain some of the conflicting effects of alcohol on the risk of different cardiovascular events [117].

5.4.2. Associations of alcohol with fatty acids

The relationships between alcohol consumption and FA subclasses were consistent with the previous study [145, 242, 256], with mostly adverse effects in relation to cardiovascular risk. Total FA, saturated FA, MUFA, omega-3 FA concentrations, saturated FA ratio, omega-3 FA ratio and DHA ratio to total FA displayed positive associations with alcohol intake; however, alcohol consumption was inversely associated with the omega-6 FA ratio, PUFA ratio and linoleic acid ratio to total FA. The predominantly adverse changes in these FA measures support higher risks of some CVD apparently associated with alcohol consumption in recent studies [117] when considered alongside studies of metabolites and risk of cardiovascular events [255].

Beer and wine consumption showed similar associations to total alcohol consumption with FA. There was, again, evidence that the consumption of beer led to a larger increase of the magnitudes in associations with a range of measures compared to the consumption of wine or total alcohol consumption, which might be due to residual confounding effects despite efforts to adjust for covariates.

We found that demographic factors including sex, age, SES and other health behaviours including smoking, diet, physical activity and CRF, but not mental health, accounted for significant increases in the associations between total alcohol consumption and FA measures compared to the unadjusted model. The interaction between diet, fitness or physical activity and alcohol with FA might be particularly important but the relationships are poorly understood.

Alcohol may influence FA by mobilising, uptake, synthesis and esterification of FA from adipose tissue [257]. Saturated FA increase LDL cholesterol, potentially increasing the risk of CVD [258]. While dietary MUFAs are protective against CVD [259-262], the MUFA ratio to total FA is a biomarker of higher cardiovascular and diabetes risk [242, 263]. Likewise, the robust association of alcohol intake with a lower proportion of omega-6 FA has been related to higher cardio-metabolic risk [242, 256, 263], noting recent findings with different effects on myocardial infarction and stroke by the influence of circulating triglycerides levels [255]. In contrast, omega-3 FA concentrations have been associated with lower cardiovascular risk [264-266]. Within the omega-3 series, the long-chain DHA are also associated with decreased coronary events, whereas the role of linolenic acid is less clear [267, 268]. In this cohort of

young adults, the weight of evidence suggests that alcohol consumption was associated with mostly harmful effects on FA that might increase cardiovascular risk later in life.

5.4.3. Associations of alcohol with low molecular weight metabolites

In line with the findings from the previous study [145], citrate and phenylalanine were strongly inversely associated with alcohol consumption, whereas they were not associated with glutamine. A strong linear association was observed for citrate, whereas phenylalanine showed a non-linear shape where the slope of the association initially declined then levelled off as alcohol consumption increased. Beer and wine consumption showed similar associations with low molecular weight metabolites as total alcohol consumption.

Alcohol might influence citrate through its effects on enzymes in oxidative pathways such as the citric acid or glyoxylate cycle that bypasses part of the citric acid cycle, including succinate dehydrogenase [269]. The effects of alcohol on phenylalanine might be related to the production of the 2-phenylethyl alcohol which is found in fresh beer or other volatiles such as ethyl alcohol [270]. In turn, higher citrate levels have been linked with modestly lower risk for CVDs [242, 271]. In contrast, higher phenylalanine has been associated with greater cardiovascular risk [242]. In this cohort, these adverse changes in citrate and phenylalanine suggest higher cardiovascular and metabolic risks related to higher alcohol consumption.

5.4.4. Strengths and limitations

The strengths of the present study are that we comprehensively examined potential linear and non-linear relationships of individual metabolite measures and alcohol consumption including different types of alcohol (noting the limited power for spirit consumption due to its infrequent consumption). Furthermore, several sensitivity analyses were performed showing the robustness of our findings. In addition, we took multiple confounding factors into account in the analysis, including diet, CRF and mental health that have not been examined in previous studies.

Our study has several limitations. The cross-sectional analyses meant that we could not confirm any casual associations between alcohol consumption and metabolites. Our young and relatively healthy cohort had few diseases and the exclusion of those with AUDs

addressed potential issues with reverse causation. Associations were unaltered when excluding non-drinkers; suggesting results were not influenced by those that stopped drinking for health reasons. Misclassification of alcohol consumption might have occurred with the FFQ. We had substantial loss to follow-up since childhood, which might affect the generalisability of our findings to other populations. However, a comparison of the CDAH sample without the metabolomics data showed similar characteristics. Furthermore, the proportion of current drinkers in the present study was very similar to that in the general Australian population [47].

5.5. Conclusion

The metabolomic signatures associated with alcohol consumption in this young adult cohort were similar to the only other existing study [198]. They suggest a diverse range of molecular processes that are both beneficial and harmful to health are related to alcohol consumption with similar effects for total consumption and different types of alcohol.

5.6. Appendix 5.A. Additional Methods

Covariates

The following covariates were considered: age, sex, socio-economic (SES) quartile base on area of residence (high, medium high, medium low, or low), region of residence (major city/urban/rural areas), education level (university, vocational, or secondary school only), occupation (professional/manager, white collar, blue collar, or not in labour force), marital status (married or living as married versus other), and smoking status (never, former, or current), collected from questionnaires. A total physical activity score (minutes per week) was calculated from the duration, intensity, and frequency of physical activity in the past week by the International Physical Activity Questionnaire (IPAQ) [181]. Cardiorespiratory fitness (CRF) was estimated as physical work capacity (PWC) at a heart rate of 170 bpm (PWC170) on a bicycle ergometer pedalled at 60 rpm [182]. CRF was then adjusted for lean body mass to create an index uncorrelated with lean body mass because of the relation between absolute workload achieved and muscle mass [220]. Dietary intakes were assessed using a food frequency questionnaire (FFQ) assessing usual frequency of intake of food excluding alcohol intake beverages over the last 12 months, and then calculated as a Dietary Guideline Index (DGI) score [272], based on recommendations in the 2003 Dietary Guidelines for Australian Adults [221] and the Australian Guide to Healthy Eating [222]. Other covariates included childhood alcohol consumption experimentation (non-drinkers or drinkers at childhood), health-related quality of life (HRQoL) (SF-12 physical and mental component scores), and depression and anxiety diagnosed in the previous 12 months by the Composite International Diagnostic Interview (CIDI) [205].

5.7. Appendix 5.B. Additional Tables and Figures

Table 5-2. Multivariable linear regression on association between total alcohol consumption by 100 grams per week and metabolite measures

	Model 1			**Model 2**		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Lipoprotein lipid concentration						
Extremely large VLDL	0.011	(-0.027, 0.050)	0.568	0.019	(-0.019, 0.057)	0.320
Very large VLDL	-0.004	(-0.048, 0.040)	0.863	0.007	(-0.034, 0.047)	0.749
Large VLDL	-0.011	(-0.058, 0.036)	0.642	-0.017	(-0.062, 0.029)	0.477
Medium VLDL	-0.042	(-0.091, 0.007)	0.091	-0.063	(-0.116, -0.010)	0.020
Small VLDL	-0.056	(-0.107, -0.005)	0.033	-0.099	(-0.158, -0.040)	0.001
Very small VLDL	-0.061	(-0.114, -0.008)	0.024	-0.083	(-0.145, -0.021)	0.01
IDL	-0.079	(-0.131, -0.026)	0.004	-0.076	(-0.139, -0.014)	0.017
Large IDL	-0.046	(-0.098, 0.006)	0.084	-0.048	(-0.109, 0.014)	0.127
Medium LDL	-0.019	(-0.070, 0.032)	0.472	-0.020	(-0.080, 0.040)	0.516
Small LDL	0.006	(-0.045, 0.057)	0.810	0.009	(-0.052, 0.069)	0.778
Very large HDL	0.064	(0.015, 0.114)	0.011	0.107	(0.053, 0.161)	0.0001
Large HDL	0.170	(0.123, 0.217)	3.03e-12	0.250	(0.194, 0.300)	<2e-16
Medium HDL	0.228	(0.180, 0.276)	<2e-16	0.270	(0.211, 0.330)	<2e-16
Small HDL	0.145	(0.097, 0.192)	3.1e-09	0.150	(0.088, 0.204)	1.0e-06
Lipoprotein particle size						

	Model 1			**Model 2**		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
VLDL particle size	-0.042	(-0.088, 0.005)	0.082	-0.059	(-0.112, -0.006)	0.028
LDL particle size	-0.123	(-0.174, -0.072)	2.6e-06	-0.130	(-0.193, -0.067)	5.8e-05
HDL particle size	0.103	(0.057, 0.148)	9.8e-06	0.153	(0.100, 0.206)	1.9e-08
Apolipoprotein						
Apolipoprotein B	-0.083	(-0.135, -0.032)	0.001	-0.093	(-0.154, -0.032)	0.003
Apolipoprotein A-1	0.188	(0.140, 0.237)	6.0e-14	0.234	(0.176, 0.291)	3.6e-15
Cholesterol						
Total C	0.027	(-0.025, 0.079)	0.312	0.046	(-0.016, 0.107)	0.145
Remnant C	-0.085	(-0.135, -0.035)	0.001	-0.092	(-0.160, -0.032)	0.003
VLDL C	-0.067	(-0.117, -0.018)	0.008	-0.085	(-0.143, -0.027)	0.004
IDL C	-0.091	(-0.143, -0.039)	0.001	-0.088	(-0.150, -0.026)	0.005
LDL C	-0.037	(-0.088, 0.015)	0.163	-0.037	(-0.098, 0.024)	0.229
HDL C	0.200	(0.152, 0.248)	4.8e-16	0.250	(0.194, 0.307)	<2e-16
HDL_2 C	0.209	(0.161, 0.257)	<2e-16	0.259	(0.202, 0.316)	<2e-16
HDL_3 C	-0.021	(-0.070, 0.028)	0.400	-0.016	(-0.074, 0.042)	0.589
Esterified C	0.035	(-0.018, 0.087)	0.193	0.052	(-0.010, 0.114)	0.097
Free C	0.006	(-0.046, 0.058)	0.816	0.024	(-0.039, 0.086)	0.435
Triglycerides						
Total TG	-0.029	(-0.080, 0.022)	0.268	-0.038	(-0.095, 0.019)	0.191
VLDL TG	-0.034	(-0.084, 0.016)	0.187	-0.049	(-0.104, 0.006)	0.083
IDL TG	-0.032	(-0.083, 0.019)	0.222	-0.033	(-0.092, 0.026)	0.271
LDL TG	-0.004	(-0.054, 0.045)	0.860	0.001	(-0.056, 0.057)	0.983

	Model 1			Model 2		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
HDL TG	0.001	(-0.050, 0.052)	0.978	0.002	(-0.055, 0.060)	0.939
Phosphatidylcholine	0.179	(0.129, 0.229)	2.1e-12	0.212	(0.154, 0.270)	1.5e-12
Sphingomyelin	0.035	(-0.016, 0.085)	0.178	0.057	(-0.002, 0.117)	0.060
Phosphoglycerides	0.178	(0.128, 0.228)	3.6e-12	0.209	(0.149, 0.268)	7.9e-12
Fatty acids						
Total FA	0.075	(0.023, 0.126)	0.005	0.881	(0.028, 0.148)	0.004
Saturated FA	0.083	(0.032, 0.135)	0.002	0.111	(0.051, 0.170)	0.001
MUFA	0.082	(0.031, 0.133)	0.002	0.070	(0.010, 0.127)	0.021
PUFA	0.038	(-0.014, 0.090)	0.148	0.064	(0.003, 0.125)	0.041
Omega-6 FA	0.025	(-0.027, 0.077)	0.342	0.047	(-0.014, 0.109)	0.133
Linoleic acid	0.011	(-0.041, 0.063)	0.676	0.029	(-0.033, 0.091)	0.358
Omega-3 FA	0.113	(0.061, 0.165)	2.1e-05	0.156	(0.096, 0.217)	4.5e-07
DHA	0.093	(0.043, 0.144)	0.001	0.125	(0.071, 0.180)	7.7e-06
Fatty acid ratios						
Saturated FA (%)	0.060	(0.007, 0.112)	0.027	0.126	(0.062, 0.188)	9.8e-05
MUFA (%)	0.078	(0.027, 0.129)	0.003	0.019	(-0.040, 0.079)	0.524
PUFA (%)	-0.115	(-0.166, -0.064)	9.8e-06	-0.087	(-0.146, -0.028)	0.004
Omega-6 FA (%)	-0.134	(-0.185, -0.083)	2.6e-07	-0.114	(-0.173, -0.055)	0.001
Linoleic acid (%)	-0.128	(-0.179, -0.077)	1.1e-06	-0.117	(-0.178, -0.057)	0.001
Omega-3 FA (%)	0.054	(0.002, 0.106)	0.042	0.095	(0.032, 0.158)	0.003
DHA (%)	0.059	(0.009, 0.108)	0.020	0.089	(0.033, 0.145)	0.002
Unsaturation Degree	-0.049	(-0.101, 0.002)	0.061	-0.010	(-0.070, 0.050)	0.739

	Model 1			**Model 2**		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Amino acids						
Alanine	0.018	(-0.035, 0.072)	0.502	0.046	(-0.018, 0.110)	0.157
Glutamine	-0.021	(-0.068, 0.027)	0.390	-0.011	(-0.067, 0.045)	0.709
Glycine	-0.081	(-0.133, -0.030)	0.002	-0.080	(-0.140, -0.020)	0.01
Branched-chain amino acids						
Isoleucine	-0.080	(-0.128, -0.032)	0.001	-0.094	(-0.150, -0.038)	0.01
Leucine	-0.015	(-0.065, 0.035)	0.562	-0.038	(-0.096, 0.021)	0.210
Valine	-0.116	(-0.165, -0.068)	2.4e-06	-0.139	(-0.197, -0.081)	2.7e-06
Aromatic amino acids						
Phenylalanine	-0.079	(-0.135, -0.024)	0.005	-0.097	(-0.167, -0.027)	0.01
Tyrosine	0.046	(-0.006, 0.098)	0.083	0.060	(-0.003, 0.122)	0.060
Histidine	-0.023	(-0.074, 0.028)	0.374	-0.032	(-0.093, 0.029)	0.306
Glycolysis and Gluconeogenesis						
Glucose	0.020	(-0.033, 0.073)	0.455	0.010	(-0.044, 0.064)	0.725
Lactate	-0.045	(-0.096, 0.007)	0.090	-0.063	(-0.125, -0.002)	0.043
Pyruvate	-0.022	(-0.075, 0.030)	0.402	-0.030	(-0.089, 0.029)	0.317
Citrate	-0.098	(-0.135, -0.061)	2.1e-07	-0.105	(-0.161, -0.049)	0.001
Glycerol	0.043	(-0.008, 0.094)	0.095	0.016	(-0.043, 0.076)	0.590
Ketone bodies						
Acetoacetate	0.019	(-0.033, 0.070)	0.473	0.019	(-0.045, 0.082)	0.564

	Model 1			Model 2		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Beta-hydroxybutyrate	0.019	(-0.032, 0.070)	0.458	0.022	(-0.040, 0.085)	0.488
Miscellaneous						
Creatinine	0.009	(-0.033, 0.051)	0.667	0.014	(-0.035, 0.063)	0.572
Albumin	0.053	(0.002, 0.105)	0.041	0.074	(0.015, 0.133)	0.015
Acetate	0.057	(0.003, 0.111)	0.038	0.049	(-0.014, 0.112)	0.129
Inflammation						
Glycoprotein acetyls	-0.038	(-0.085, 0.009)	0.109	-0.020	(-0.074, 0.034)	0.474

CI, confidence interval; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; TG, triglycerides; FA, fatty acid; DHA, docosahexaenoic acid.

Model 1 adjusted for sex, age. Model 2 adjusted for Model 1 + region, SES status, educational level, occupation, marital status, smoking, diet, physical activity, cardiorespiratory fitness, depression and anxiety.

† β=beta coefficients expressed in standard deviation unit change per 100 grams of alcohol consumption per week

Table 5-3. Multivariable polynomial regression on the non-linear associations between total alcohol consumption by 100 grams per week and metabolite measures

		Model 1			Model 2		
	N	**β †**	**95% CI**	**p-value**	**β †**	**95% CI**	**p-value**
Lipoprotein lipid concentration							
Medium VLDL	1,740	-0.036	(-0.056, -0.016)	<0.001	-0.017	(-0.033, -0.001)	0.034
Small VLDL	1,758	-0.122	(-0.178, -0.067)	<0.001	-0.119	(-0.183, -0.056)	<0.001
Large HDL	1,758	0.296	(0.224, 0.369)	<0.001	0.373	(0.292, 0.453)	<0.001
Medium HDL	1,758	0.378	(0.311, 0.446)	<0.001			
Small HDL	1,758	0.202	(0.133, 0.271)	<0.001	0.199	(0.115, 0.283)	<0.001
Lipoprotein particle size							
HDL particle size	1,759	0.001	(-0.073, 0.073)	0.400	0.271	(0.194, 0.348)	<0.001
Apolipoprotein							
Apolipoprotein A-1	1,783	0.321	(0.245, 0.397)	<0.001	0.379	(0.290, 0.469)	<0.001
Cholesterol							
HDL C	1,767	0.354	(0.276, 0.431)	<0.001	0.415	(0.324, 0.506)	<0.001
HDL_2 C	1,783	0.373	(0.295, 0.450)	<0.001	0.432	(0.340, 0.523)	<0.001
Triglycerides							
Phosphatidylcholine	1,765	0.290	(0.213, 0.368)	<0.001	0.325	(0.235, 0.414)	<0.001
Phosphoglycerides	1,766	0.277	(0.200, 0.354)	<0.001	0.316	(0.226, 0.406)	<0.001
Fatty acids							
Saturated FA	1,766	0.118	(0.041, 0.182)	0.001	0.147	(0.066, 0.228)	<0.001

		Model 1			Model 2		
	N	**β †**	**95% CI**	**p-value**	**β †**	**95% CI**	**p-value**
Omega-3 FA	1,766	0.179	(0.103, 0.254)	<0.001	0.211	(0.125, 0.297)	<0.001
DHA	1,766	0.190	(0.111, 0.269)	<0.001	0.213	(0.129, 0.297)	<0.001
Fatty acid ratios							
Saturated FA (%)	1,766	0.088	(0.014, 0.162)	0.020	0.162	(0.075, 0.249)	<0.001
Omega-6 FA (%)	1,765	-0.103	(-0.172, -0.033)	0.001	-0.118	(-0.198, -0.038)	0.004
Linoleic acid (%)	1,766	-0.128	(-0.200, -0.055)	<0.001			
DHA (%)	1,766	0.165	(0.088, 0.243)	<0.001	0.182	(0.098, 0.267)	<0.001
Amino acids							
Branched-chain amino acids							
Valine	1,739	-0.114	(-0.173, -0.055)	<0.001	-0.154	(-0.224, -0.084)	<0.001
Glycolysis and Gluconeogenesis							
Citrate	1,772	-0.134	(-0.185, -0.083)	<0.001	-0.129	(-0.188, -0.069)	<0.001

CI, confidence interval; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; TG, triglycerides; FA, fatty acid; DHA, docosahexaenoic acid.

Model 1 adjusted for sex, age. Model 2 adjusted for Model 1 + region, SES status, educational level, occupation, marital status, smoking, diet, physical activity, cardiorespiratory fitness, depression and anxiety.

† β=beta coefficients expressed in standard deviation unit change per 100 grams of alcohol consumption per week

Table 5-4. Multivariable linear regression models on association between total alcohol consumption by 100 grams per week and metabolite measures

		Unadjusted			Adjusted								
					Model 1			Model 2			Model 3		
	N	β†	95% CI	p-value	β†	95% CI	p-value	β†	95% CI	p-value	β†	95% CI	p-value
Lipoprotein lipid concentration													
Log(Large HDL)	1,758	0.083	(0.000, 0.001)	0.0006	0.180	(0.134, 0.225)	1.7e-14	0.250	(0.196, 0.301)	<2e-16	0.250	(0.194, 0.300)	<2e-16
Medium HDL	1,758	0.150	(0.100, 0.199)	4.4e-09	0.223	(0.175, 0.272)	<2e-16	0.270	(0.211, 0.330)	<2e-16	0.270	(0.211, 0.330)	<2e-16
Small HDL	1,758	0.167	(0.008, 0.015)	2.84e-11	0.141	(0.093, 0.190)	1.1e-08	0.142	(0.084, 0.200)	1.8e-06	0.150	(0.088, 0.204)	1.0e-06
Lipoprotein particle size													
LDL particle size	1,758	-0.128	(-0.178, -0.078)	5.66e-07	-0.115	(-0.167, -0.064)	1.1e-05	-0.125	(-0.187, -0.062)	0.0001	-0.130	(-0.193, -0.067)	5.8e-05
HDL particle size	1,759	-0.008	(-0.058, 0.042)	0.7539	0.100	(0.053, 0.145)	2.3e-05	0.157	(0.104, 0.209)	7.5e-09	0.153	(0.100, 0.206)	1.9e-08
Apolipoprotein													
Apolipoprotein A-1	1,783	0.136	(0.087, 0.186)	8.56e-08	0.185	(0.136, 0.234)	2.6e-13	0.231	(0.174, 0.289)	4.9e-15	0.234	(0.176, 0.291)	3.6e-15
Cholesterol													

		Unadjusted			Adjusted								
					Model 1			Model 2			Model 3		
	N	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Remnant C	1,761	-0.063	(-0.113, -0.014)	0.0125	-0.077	(-0.128, -0.026)	0.0030	-0.091	(-0.151, -0.031)	0.0029	-0.092	(-0.160, -0.032)	0.0028
IDL C	1,758	-0.074	(-0.124, -0.024)	0.0037	-0.083	(-0.136, -0.031)	0.0019	-0.088	(-0.150, -0.027)	0.0051	-0.088	(-0.150, -0.026)	0.0054
HDL C	1,767	0.129	(0.080, 0.180)	3.89e-07	0.195	(0.147, 0.243)	4.1e-15	0.249	(0.193, 0.305)	<2e-16	0.250	(0.194, 0.055)	<2e-16
HDL_2 C	1,783	0.131	(0.081, 0.181)	3.03e-07	0.203	(0.154, 0.251)	4.0e-16	0.258	(0.202, 0.315)	<2e-16	0.259	(0.202, 0.316)	<2e-16
Triglycerides													
Phosphatidylcholine	1,765	0.130	(0.081, 0.180)	3.09e-07	0.179	(0.128, 0.229)	4.8e-12	0.211	(0.153, 0.269)	1.4e-12	0.212	(0.154, 0.270)	1.5e-12
Phosphoglycerides	1,766	0.134	(0.084, 0.183)	1.46e-07	0.178	(0.128, 0.229)	7e-12	0.207	(0.148, 0.266)	8.7e-12	0.209	(0.149, 0.268)	7.9e-12
Fatty acids													
Total FA	1,766	0.078	(0.028, 0.128)	0.0021	0.079	(0.027, 0.132)	0.003	0.086	(0.026, 0.145)	0.005	0.081	(0.028, 0.148)	0.004
Log(Saturated FA)	1,766	0.090	(0.043, 0.137)	0.0002	0.097	(0.046, 0.147)	0.002	0.118	(0.060, 0.175)	7.1e-05	0.121	(0.063, 0.179)	5.0e-05
Log(MUFA)	1,766	0.093	(0.046, 0.139)	0.0001	0.086	(0.036, 0.136)	0.001	0.069	(0.012, 0.127)	0.018	0.070	(0.012, 0.129)	0.018
Omega-3 FA	1,766	0.104	(0.054, 0.154)	5.1e-05	0.111	(0.059, 0.164)	3.2e-05	0.154	(0.094, 0.214)	6.0e-07	0.156	(0.096, 0.217)	4.5e-07
DHA	1,766	0.038	(-0.012, 0.088)	0.135	0.086	(0.036, 0.137)	0.0001	0.123	(0.069, 0.178)	9.6e-06	0.125	(0.071, 0.180)	7.7e-06

		Unadjusted			Adjusted								
					Model 1			Model 2			Model 3		
	N	β†	95% CI	p-value	β†	95% CI	p-value	β†	95% CI	p-value	β†	95% CI	p-value
Fatty acid ratios													
Saturated FA (%)	1,766	0.054	(0.004, 0.104)	0.0349	0.059	(0.006, 0.112)	0.030	0.123	(0.060, 0.186)	0.0001	0.126	(0.062, 0.188)	9.8e-05
MUFA (%)	1,766	0.118	(0.068, 0.168)	3.58e-06	0.089	(0.038, 0.139)	0.001	0.020	(-0.039, 0.079)	0.511	0.019	(-0.040, 0.079)	0.524
PUFA (%)	1,766	-0.154	(-0.204, -0.105)	1.17e-09	-0.126	(-0.176, -0.075)	1.3e-06	-0.087	(-0.145, -0.028)	0.004	-0.087	(-0.146, -0.028)	0.004
Omega-6 FA (%)	1,765	-0.172	(-0.221, -0.122)	1.16e-11	-0.143	(-0.194, -0.092)	3.9e-08	-0.113	(-0.171, -0.054)	0.002	-0.114	(-0.173, -0.055)	0.001
Linoleic acid (%)	1,766	-0.159	(-0.209, -0.109)	3.89e-10	-0.137	(-0.189, -0.086)	1.8e-07	-0.118	(-0.178, -0.058)	0.001	-0.117	(-0.178, -0.057)	0.001
Log(DHA (%))	1,766	0.016	(-0.031, 0.063)	0.509	0.046	(-0.003, 0.095)	0.064	0.088	(0.032, 0.144)	0.002	0.089	(0.033, 0.145)	0.002
Amino acids													
Glycine	1,728	-0.109	(-0.160, -0.058)	3.21e-05	-0.079	(-0.131, -0.027)	0.003	-0.077	(-0.137, -0.017)	0.012	-0.080	(-0.140, -0.020)	0.01
Branched-chain amino acids													
Isoleucine	1,778	-0.002	(-0.052, 0.049)	0.9510	-0.081	(-0.130, -0.032)	0.01	-0.092	(-0.149, -0.036)	0.001	-0.094	(-0.150, -0.038)	0.01
Valine	1,739	-0.027	(-0.078, 0.024)	0.3030	-0.114	(-0.163, -0.066)	4.6e-06	-0.139	(-1.964, -0.081)	2.7e-06	-0.139	(-0.197, -0.081)	2.7e-06

		Unadjusted			Adjusted								
					Model 1			Model 2			Model 3		
	N	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Aromatic amino acids													
Phenylalaine	1,766	-0.092	(-0.140, -0.045)	0.0002	-0.075	(-0.131, -0.019)	0.01	-0.094	(-0.164, -0.025)	0.01	-0.097	(-0.167, -0.027)	0.01
Glycolysis and Gluconeogenesis													
Citrate	1,772	-0.109	(-0.155, -0.062)	4.96e-06	-0.122	(-0.171, -0.074)	9.5e-07	-0.099	(-0.155, -0.043)	0.001	-0.105	(-0.161, -0.049)	0.001

CI, confidence interval; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; TG, triglycerides; FA, fatty acid; DHA, docosahexaenoic acid.

Model 1 adjusted for sex, age, region, SES status, educational level, occupation, marital status. Model 2 adjusted for Model 1 + smoking, diet, physical activity, cardiorespiratory fitness. Model 3 adjusted for Model 2 + depression and anxiety.

† β=beta coefficients expressed in standard deviation unit change per 100 grams of alcohol consumption per week

Table 5-5. Multivariable linear regression models examining the interaction between total alcohol consumption by 100 grams per week and covariates on metabolite measures

		Unadjusted			Adjusted		
	N	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Lipoprotein lipid concentration							
Log(Large HDL)	1,756						
Alc (100g/week)		0.218	(0.145, 0.291)	6.0e-09	0.285	(0.202, 0.368)	2.3e-11
Sex (male)		-0.818	(-0.924, -0.713)	<2e-16	-0.769	(-0.926, -0.611)	<2e-16
Alc x Sex		-0.105	(-0.199, -0.011)	0.028	-0.135	(-0.243, -0.026)	0.015
Log(Large HDL)	1,407						
Alc (100g/week)		0.322	(0.162, 0.482)	8.3e-05	0.393	(0.234, 0.551)	1.4e-06
Pwc170		-0.004	(-0.005, -0.003)	2.3e-13	0.001	(-4e-04, 0.003)	0.154
Alc x Pwc170		-0.001	(-0.002, -3e-05)	0.043	-0.001	(-0.002, -0.001)	0.016
Log(Large HDL)	1,556						
Alc (100g/week)		0.062	(0.004, 0.119)	0.035	0.192	(0.131, 0.253)	1.0e-09
Depression/anxiety		0.116	(-0.047, 0.278)	0.163	0.019	(-0.148, 0.186)	0.826
Alc x Dep/Anx		0.191	(0.047, 0.335)	0.009	0.085	(-0.052, 0.223)	0.224
Medium HDL	1,556						
Alc (100g/week)		0.134	(0.076, 0.192)	5.8e-06	0.265	(0.201, 0.329)	9.6e-16
Depression/anxiety		0.010	(-0.153, 0.174)	0.900	-0.109	(-0.283, 0.065)	0.220
Alc x Dep/Anx		0.159	(0.014, 0.304)	0.032	0.021	(-0.123, 0.164)	0.777

		Unadjusted			Adjusted		
	N	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Lipoprotein particle size							
LDL particle size	1,756						
Alc (100g/week)		-0.194	(-0.275, -0.113)	2.7e-06	-0.177	(-0.272, -0.082)	0.001
Sex (male)		-0.063	(-0.179, 0.053)	0.288	0.097	(-0.084, 0.277)	0.293
Alc x Sex		0.108	(0.004, 0.211)	0.042	0.083	(-0.041, 0.208)	0.190
LDL particle size	1,639						
Alc (100g/week)		-0.082	(-0.148, -0.016)	0.014	-0.066	(-0.145, 0.013)	0.104
Smoking		-0.037	(-0.183, 0.109)	0.620	-0.041	(-0.218, 0.136)	0.648
Alc x Smoking		-0.114	(-0.222, -0.006)	0.038	-0.169	(-0.297, -0.041)	0.010
LDL particle size	1,407						
Alc (100g/week)		-0.339	(-0.509, -0.171)	8e-05	-0.309	(-0.491, -0.127)	0.001
Pwc170		-0.001	(-0.002, 2.6e-05)	0.055	-0.002	(-0.003, 0.001)	0.078
Alc x Pwc170		0.001	(0.001, 2.2e-03)	0.005	0.001	(5.1e-05, 0.002)	0.040
HDL particle size	1,557						
Alc (100g/week)		-0.008	(-0.065, -0.008)	0.792	0.139	(0.081, 0.198)	3.6e-06
Depression/anxiety		0.133	(-0.030, 0.295)	0.109	-0.019	(-0.180, 0.141)	0.813
Alc x Dep/Anx		0.147	(0.004, 0.291)	0.045	0.070	(-0.062, 0.202)	0.301
Cholesterol							
HDL C	1,765						
Alc (100g/week)		0.258	(0.182, 0.242)	4.0e-11	0.302	(0.216, 0.387)	5.8e-12

		Unadjusted			Adjusted		
	N	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Sex(male)		-0.630	(-0.740, -0.521)	<2e-16	-0.689	(-0.851, -0.528)	<2e-16
Alc x Sex		-0.103	(-0.201, -0005)	0.039	-0.090	(-0.201, 0.022)	0.116
HDL C	1,565						
Alc (100g/week)		0.100	(-0.060, 0.071)	0.001	0.228	(0.165, 0.290)	1.6e-12
Depression/anxiety		0.006	(-0.154, 0.166)	0.944	-0.083	(-0.253, 0.087)	0.339
Alc x Dep/Anx		0.246	(0.104, 0.388)	0.001	0.119	(-0.022, 0.259)	0.098
HDL_2 C	1,783						
Alc (100g/week)		0.266	(0.190, 0.341)	2.2e-07	0.313	(0.227, 0.398)	1.2e-12
Sex(male)		-0.675	(-0.783, -0.567)	<2e-16	-0.735	(-0.897, -0.573)	<2e-16
Alc x Sex		-0.104	(-0.201, -0.007)	0.036	-0.094	(-0.206, 0.018)	0.100
HDL_2 C	1,431						
Alc (100g/week)		0.356	(0.193, 0.519)	1.9e-05	0.417	(0.253, 0.581)	6.7e-07
Pwc170		-0.004	(-0.005, -0.002)	1.4e-09	0.001	(-0.001, 0.003)	0.165
Alc x Pwc170		-0.001	(-0.002, -0.001)	0.047	-0.001	(-0.002, -0.001)	0.044
HDL_2 C	1,581						
Alc (100g/week)		0.104	(0.046, 0.161)	0.001	0.238	(0.175, 0.040)	2e-13
Depression/anxiety		0.012	(-0.149, 0.173)	0.885	-0.082	(-0.252, 0.087)	0.341
Alc x Dep/Anx		0.240	(0.096, 0.384)	0.001	0.109	(-0.033, 0.250)	0.131
Triglycerides							
Phosphatidylcholine	1,563						

		Unadjusted			Adjusted		
	N	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Alc (100g/week)		0.107	(0.050, 0.164)	0.001	0.192	(0.128, 0.257)	6.8e-09
Depression/anxiety		-0.082	(-0.243, 0.080)	0.321	-0.154	(-0.329, 0.022)	0.086
Alc x Dep/Anx		0.199	(0.056, 0.342)	0.006	0.104	(-0.041, 0.250)	0.159
Phosphoglycerides	1,564						
Alc (100g/week)		0.110	(0.053, 0.168)	0.001	0.190	(0.124, 0.256)	1.7e-08
Depression/anxiety		-0.080	(-0.242, 0.081)	0.330	-0.141	(-0.320, 0.037)	0.120
Alc x Dep/Anx		0.191	(0.048, 0.334)	0.009	0.096	(-0.052, 0.244)	0.203
Fatty acids							
Omega-3 FA	1,647						
Alc (100g/week)		0.169	(-0.162, -0.030)	3.5e-07	0.221	(0.145, 0.296)	1.5e-08
Smoking		-0.014	(-0.157, 0.130)	0.852	0.160	(-0.010, 0.329)	0.065
Alc x Smoking		-0.123	(-0.229, -0.017)	0.023	-0.171	(-0.293, -0.048)	0.006
Fatty acid ratios							
Saturated FA (%)	1,414						
Alc (100g/week)		0.330	(0.158, 0.501)	0.001	0.298	(0.116, 0.479)	0.001
Pwc170		0.002	(0.001, 0.003)	0.006	0.002	(-0.001, 0.003)	0.089
Alc x Pwc170		-0.001	(-0.002, -0.001)	0.005	-0.001	(-0.002, -0.000)	0.048
PUFA (%)	1,740						
Alc (100g/week)		-0.062	(-0.166, 0.043)	0.250	-0.056	(-0.179, 0.067)	0.375
Occupation		-0.048	(-0.100, 0.004)	0.707	-0.015	(-0.080, 0.050)	0.654

		Unadjusted			Adjusted		
	N	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Alc x Occupation		-0.045	(-0.089, -0.001)	0.047	-0.015	(-0.066, 0.036)	0.565
Amino acids							
Glycine	1,726						
Alc (100g/week)		-0.156	(-0.236, -0.076)	0.001	-0.151	(-0.241, -0.061)	0.001
Sex		-0.468	(-0.583, -0.352)	4.6e-15	-0.426	(-0.589, -0.253)	1.5e-06
Alc x Sex		0.138	(0.034, 0.241)	0.009	0.127	(0.007, 0.245)	0.037
Glycine	1,726						
Alc (100g/week)		0.544	(-0.106, 1.194)	0.101	1.188	(0.435, 1.942)	0.002
Age		0.039	(0.016, 0.063)	0.001	0.042	(0.015, 0.069)	0.002
Alc x Age		-0.021	(-0.041, -0.001)	0.047	-0.040	(-0.064, -0.016)	0.001
Glycine	1,722						
Alc (100g/week)		0.015	(-0.111, 0.141)	0.819	0.044	(-0.098, 0.185)	0.547
Education		0.120	(0.049, 0.191)	0.001	0.143	(0.053, 0.233)	0.002
Alc x Education		-0.066	(-0.127, -0.004)	0.037	-0.070	(-0.142, 0.003)	0.059
Glycine	1,702						
Alc (100g/week)		0.008	(-0.101, 0.117)	0.887	0.064	(-0.061, 0.188)	0.315
Occupation		0.118	(0.065, 0.171)	1.5e-05	0.107	(0.040, 0.173)	0.002
Alc x Occupation		-0.056	(-0.102, -0.011)	0.017	-0.068	(-0.120, -0.016)	0.010
Glycine	1,387						
Alc (100g/week)		-0.307	(-0.474, -0.140)	0.001	-0.270	(-0.442, -0.097)	0.002

		Unadjusted			**Adjusted**		
	N	**β†**	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Pwc170		-0.003	(-0.004, -0.002)	2.2e-06	-0.001	(-0.002, 0.001)	0.467
Alc x Pwc170		0.001	(0.001, 0.002)	0.012	0.001	(0.001, 0.002)	0.022
Branched-chain amino acids							
Valine	1,737						
Alc (100g/week)		0.054	(-0.051, 0.039)	0.314	-0.109	(-0.225, 0.008)	0.069
Drink before test		0.164	(0.034, 0.294)	0.014	0.011	(-0.133, 0.155)	0.878
Alc x Drink before test		-0.134	(-0.258, -0.011)	0.033	-0.039	(-0.175, 0.097)	0.574
Valine	1,688						
Alc (100g/week)		-0.335	(-0.599, -0.071)	0.013	-0.315	(-0.618, -0.011)	0.042
Diet		-0.009	(-0.012, -0.006)	2.1e-08	-0.003	(-0.007, 0.001)	0.082
Alc x Diet		0.003	(0.001, 0.006)	0.027	0.002	(-0.001, 0.006)	0.248
Glycolysis and Gluconeogenesis							
Citrate	1,770						
Alc (100g/week)		-0.165	(-0.271, -0.059)	0.002	-0.209	(-0.296, -0.122)	2.9e-06
Drink before test		-0.165	(-0.296, -0.034)	0.013	-0.174	(-0.282, -0.066)	0.002
Alc x Drink before test		0.129	(0.005, 0.253)	0.041	0.186	(0.084, 0.288)	0.001

CI=confidence interval; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; TG, triglycerides; FA, fatty acid; DHA, docosahexaenoic acid.

Model adjusted for sex, age, region, SES status, educational level, occupation, marital status, smoking, diet, physical activity, cardiorespiratory fitness, depression and anxiety.

† β=beta coefficients expressed in standard deviation unit change per 100 grams of alcohol consumption per week

Table 5-6. Sensitivity analysis of the association between total alcohol consumption by 100 grams per week and metabolite measures after excluding participants with alcohol use disorders (AUDs)

	All participants			**Excluding those with an AUD**		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Lipoprotein lipid concentration						
Extremely large VLDL	0.019	(-0.019, 0.057)	0.320	0.015	(-0.028, 0.058)	0.494
Very large VLDL	0.007	(-0.034, 0.047)	0.749	0.006	(-0.039, 0.050)	0.800
Large VLDL	-0.017	(-0.062, 0.029)	0.477	-0.010	(-0.060, 0.041)	0.717
Medium VLDL	-0.063	(-0.116, -0.010)	0.020	-0.056	(-0.114, -0.033)	0.040
Small VLDL	-0.099	(-0.158, -0.040)	0.001	-0.102	(-0.169, -0.037)	0.001
Very small VLDL	-0.083	(-0.145, -0.021)	0.01	-0.090	(-0.162, -0.020)	0.012
IDL	-0.076	(-0.139, -0.014)	0.017	-0.072	(-0.153, -0.009)	0.024
Large IDL	-0.048	(-0.109, 0.014)	0.127	-0.035	(-0.115, 0.044)	0.387
Medium LDL	-0.020	(-0.080, 0.040)	0.516	-0.010	(-0.086, 0.072)	0.860
Small LDL	0.009	(-0.052, 0.069)	0.778	0.024	(-0.054, 0.104)	0.538
Very large HDL	0.107	(0.053, 0.161)	0.0001	0.123	(0.053, 0.194)	0.0006
Large HDL	0.250	(0.194, 0.300)	<2e-16	0.276	(0.215, 0.336)	<2e-16
Medium HDL	0.270	(0.211, 0.330)	<2e-16	0.303	(0.228, 0.379)	<2e-16

	All participants			Excluding those with an AUD		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Small HDL	0.150	(0.088, 0.204)	1.0e-06	0.134	(0.057, 0.210)	0.0006
Lipoprotein particle size						
VLDL particle size	-0.059	(-0.112, -0.006)	0.028	-0.066	(-0.136, -0.001)	0.048
LDL particle size	-0.130	(-0.193, -0.067)	5.8e-05	-0.139	(-0.221, -0.056)	0.0009
HDL particle size	0.153	(0.100, 0.206)	1.9e-08	0.202	(0.133, 0.271)	1.9e-08
Apolipoprotein						
Apolipoprotein B	-0.093	(-0.154, -0.032)	0.003	-0.089	(-0.168, -0.011)	0.026
Apolipoprotein A-1	0.234	(0.176, 0.291)	3.6e-15	0.261	(0.186, 0.337)	1.7e-11
Cholesterol						
Total C	0.046	(-0.016, 0.107)	0.145	0.069	(-0.011, 0.149)	0.090
Remnant C	-0.092	(-0.160, -0.032)	0.003	-0.091	(-0.168, -0.013)	0.022
VLDL C	-0.085	(-0.143, -0.027)	0.004	-0.090	(-0.166, -0.015)	0.018
IDL C	-0.088	(-0.150, -0.026)	0.005	-0.078	(-0.158, 0.002)	0.057
LDL C	-0.037	(-0.098, 0.024)	0.229	-0.022	(-0.101, 0.057)	0.590
HDL C	0.250	(0.194, 0.307)	<2e-16	0.283	(0.209, 0.356)	1.4e-13
HDL_2 C	0.259	(0.202, 0.316)	<2e-16	0.297	(0.223, 0.371)	7.6e-15
HDL_3 C	-0.016	(-0.074, 0.042)	0.589	-0.054	(-0.130, 0.021)	0.159
Esterified C	0.052	(-0.010, 0.114)	0.097	0.077	(-0.003, 0.157)	0.060
Free C	0.024	(-0.039, 0.086)	0.435	0.042	(-0.037, 0.123)	0.293
Triglycerides						
Total TG	-0.038	(-0.095, 0.019)	0.191	-0.047	(-0.120, 0.027)	0.212

	All participants			**Excluding those with an AUD**		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
VLDL TG	-0.049	(-0.104, 0.006)	0.083	-0.055	(-0.125, 0.016)	0.128
IDL TG	-0.033	(-0.092, 0.026)	0.271	-0.050	(-0.126, 0.027)	0.202
LDL TG	0.001	(-0.056, 0.057)	0.983	-0.004	(-0.077, 0.069)	0.916
HDL TG	0.002	(-0.055, 0.060)	0.939	-0.009	(-0.085, 0.066)	0.810
Phosphatidylcholine	0.212	(0.154, 0.270)	1.5e-12	0.235	(0.159, 0.311)	2.0e-09
Sphingomyein	0.057	(-0.002, 0.117)	0.060	0.068	(-0.011, 0.146)	0.091
Phosphoglycerides	0.209	(0.149, 0.268)	7.9e-12	0.233	(0.156, 0.311)	4.9e-09
Fatty acids						
Total FA	0.881	(0.028, 0.148)	0.004	0.901	(0.013, 0.167)	0.022
Saturated FA	0.111	(0.051, 0.170)	0.001	0.113	(0.036, 0.190)	0.002
MUFA	0.070	(0.010, 0.127)	0.021	0.067	(0.008, 0.141)	0.041
PUFA	0.064	(0.003, 0.125)	0.041	0.070	(0.001, 0.142)	0.050
Omega-6 FA	0.047	(-0.014, 0.109)	0.133	0.054	(-0.026, 0.134)	0.186
Linoleic acid	0.029	(-0.033, 0.091)	0.358	0.036	(-0.045, 0.116)	0.387
Omega-3 FA	0.156	(0.096, 0.217)	4.5e-07	0.154	(0.077, 0.232)	0.0001
DHA	0.125	(0.071, 0.180)	7.7e-06	0.125	(0.058, 0.201)	0.0004
Fatty acid ratios						
Saturated FA (%)	0.126	(0.062, 0.188)	9.8e-05	0.136	(0.054, 0.217)	0.001
MUFA (%)	0.019	(-0.040, 0.079)	0.524	0.009	(-0.068, 0.086)	0.820
PUFA (%)	-0.087	(-0.146, -0.028)	0.004	-0.082	(-0.158, -0.006)	0.030
Omega-6 FA (%)	-0.114	(-0.173, -0.055)	0.001	-0.107	(-0.182, -0.032)	0.002
Linoleic acid (%)	-0.117	(-0.178, -0.057)	0.001	-0.115	(-0.192, -0.037)	0.002

	All participants			**Excluding those with an AUD**		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Omega-3 FA (%)	0.095	(0.032, 0.158)	0.003	0.091	(0.010, 0.173)	0.003
DHA (%)	0.089	(0.033, 0.145)	0.002	0.097	(0.023, 0.170)	0.009
Unsaturation Degree	-0.010	(-0.070, 0.050)	0.739	-0.014	(-0.092, 0.064)	0.725
Amino acids						
Alanine	0.046	(-0.018, 0.110)	0.157	0.048	(-0.036, 0.131)	0.266
Glutamine	-0.011	(-0.067, 0.045)	0.709	-0.008	(-0.081, 0.065)	0.831
Glycine	-0.080	(-0.140, -0.020)	0.01	-0.096	(-0.176, -0.016)	0.019
Branched-chain amino acids						
Isoleucine	-0.094	(-0.150, -0.038)	0.01	-0.124	(-0.196, -0.052)	0.001
Leucine	-0.038	(-0.096, 0.021)	0.210	-0.054	(-0.130, 0.021)	0.159
Valine	-0.139	(-0.197, -0.081)	2.7e-06	-0.166	(-0.241, -0.091)	1.6e-05
Aromatic amino acids						
Phenylalaine	-0.097	(-0.167, -0.027)	0.01	-0.118	(-0.214, -0.022)	0.016
Tyrosine	0.060	(-0.003, 0.122)	0.060	0.075	(-0.008, 0.158)	0.076
Histidine	-0.032	(-0.093, 0.029)	0.306	-0.056	(-0.137, 0.024)	0.168
Glycolysis and Gluconeogenesis						
Glucose	0.010	(-0.044, 0.064)	0.725	0.043	(-0.030, 0.115)	0.251
Lactate	-0.063	(-0.125, -0.002)	0.043	-0.067	(-0.148, 0.015)	0.108
Pyruvate	-0.030	(-0.089, 0.029)	0.317	-0.019	(-0.097, 0.059)	0.631
Citrate	-0.105	(-0.161, -0.049)	0.001	-0.113	(-0.177, -0.048)	0.001

	All participants			Excluding those with an AUD		
	β†	**95% CI**	**p-value**	**β†**	**95% CI**	**p-value**
Glycerol	0.016	(-0.043, 0.076)	0.590	0.007	(-0.070, 0.085)	0.852
Ketone bodies						
Acetoacetate	0.019	(-0.045, 0.082)	0.564	0.002	(-0.079, 0.082)	0.969
Beta-hydroxybutyrate	0.022	(-0.040, 0.085)	0.488	0.022	(-0.102, 0.058)	0.594
Miscellaneous						
Creatinine	0.014	(-0.035, 0.063)	0.572	0.016	(-0.081, 0.049)	0.629
Albumin	0.074	(0.015, 0.133)	0.015	0.148	(0.070, 0.226)	0.001
Acetate	0.049	(-0.014, 0.112)	0.129	0.064	(-0.017, 0.145)	0.123
Inflammation						
Glycoprotein acetyls	-0.020	(-0.074, 0.034)	0.474	-0.021	(-0.091, 0.049)	0.560

CI=confidence interval; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; IDL, intermediate-density lipoprotein; HDL, high-density lipoprotein; C, cholesterol; TG, triglycerides; FA, fatty acid; DHA, docosahexaenoic acid.

Model 1 adjusted for sex, age. Model 2 adjusted for Model 1 + region, SES status, educational level, occupation, marital status, smoking, diet, physical activity, cardiorespiratory fitness, depression and anxiety.

† β=beta coefficients expressed in standard deviation unit change per 100 grams of alcohol consumption per week

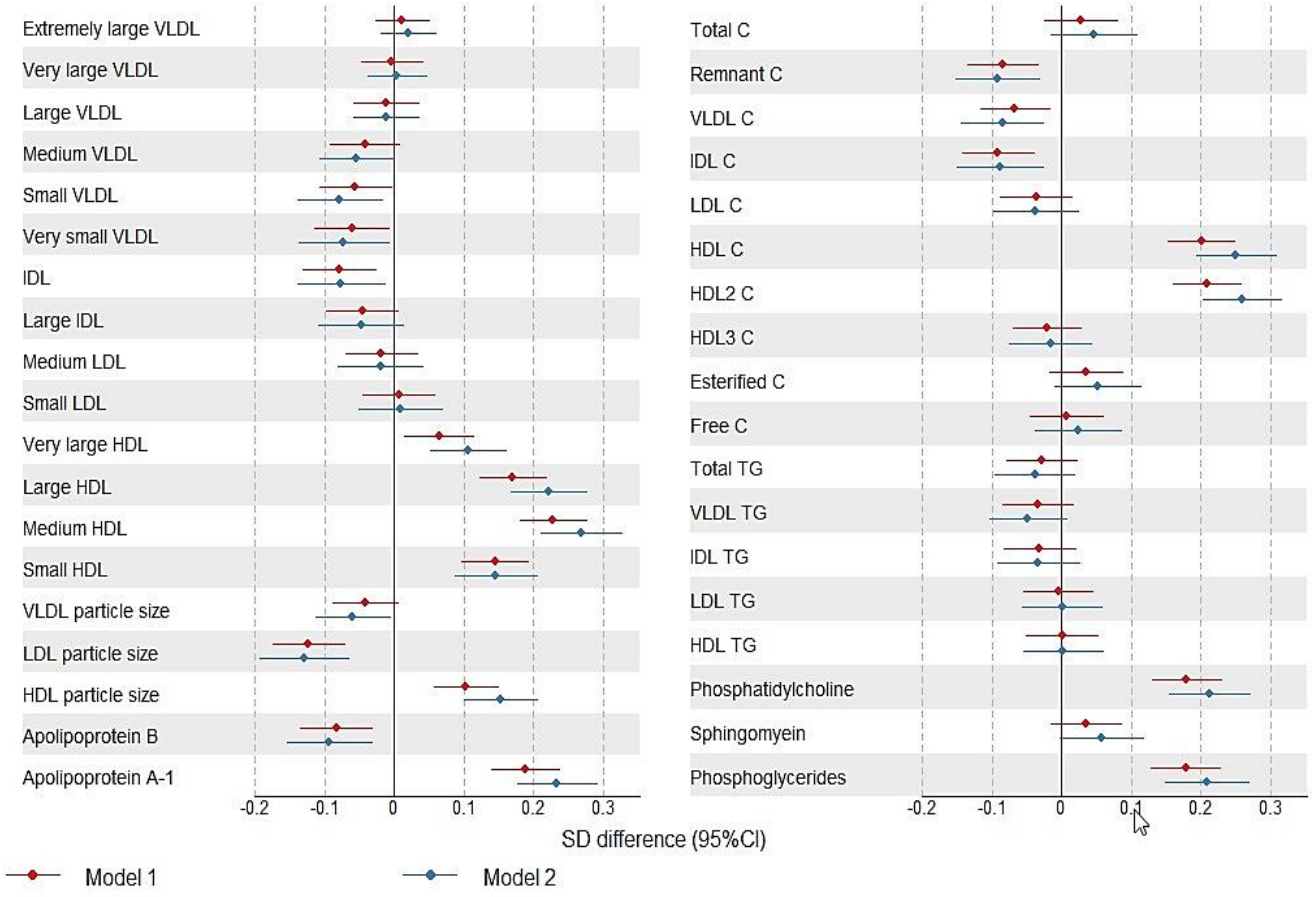


Figure 5-5. Cross-sectional associations between alcohol consumption (100 grams of pure alcohol per week) and lipoprotein lipid measures.

All association were adjusted for age and sex in Model 1; and Model 1 plus region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 100 grams of alcohol per week. Association magnitudes in absolute concentration units are listed in Appendix Table 5-2 and continuous shapes of the metabolic associations with alcohol intake are shown in Appendix Figure 5-14 to Figure 5-16.

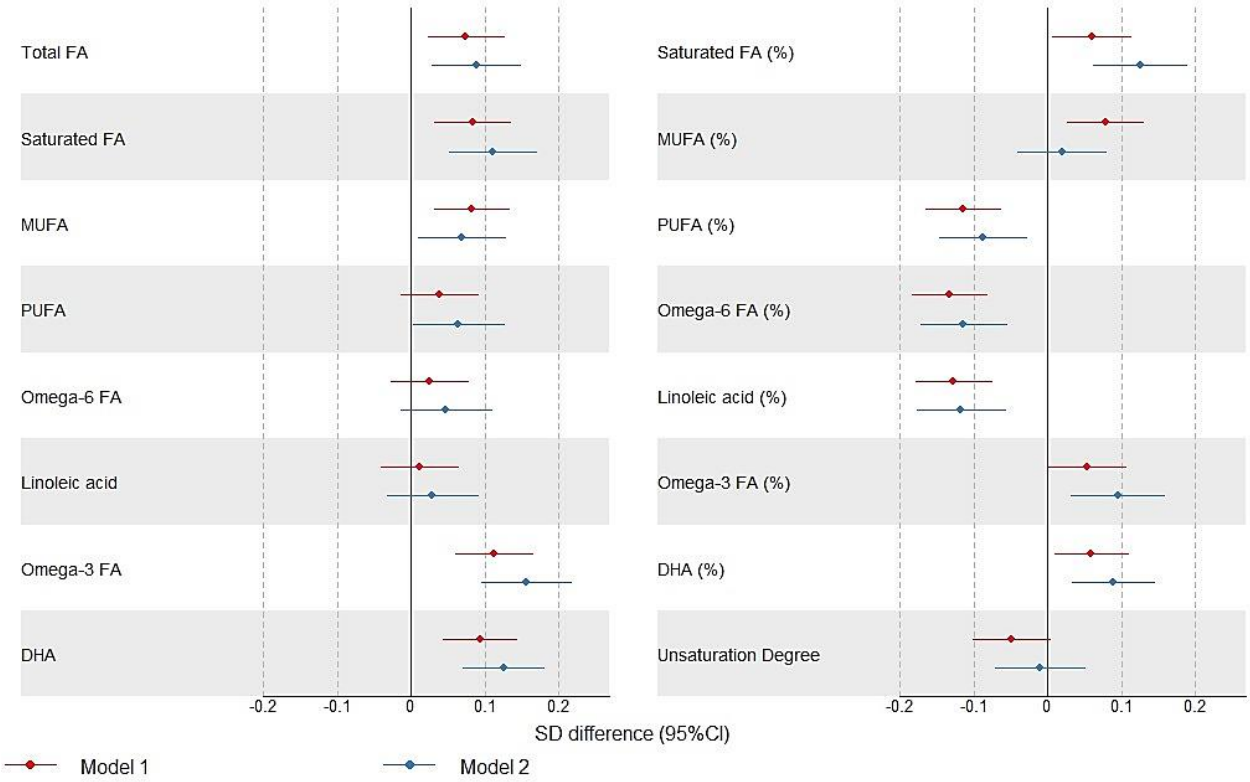


Figure 5-6. Cross-sectional associations between alcohol consumption and fatty acids.

All association were adjusted for age and sex in Model 1; and Model 1 plus region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 100 grams of alcohol per week. Association magnitudes in absolute concentration units are listed in Appendix Table 5-2 and continuous shapes of the metabolic associations with alcohol intake are shown in Appendix Figure 5-17.

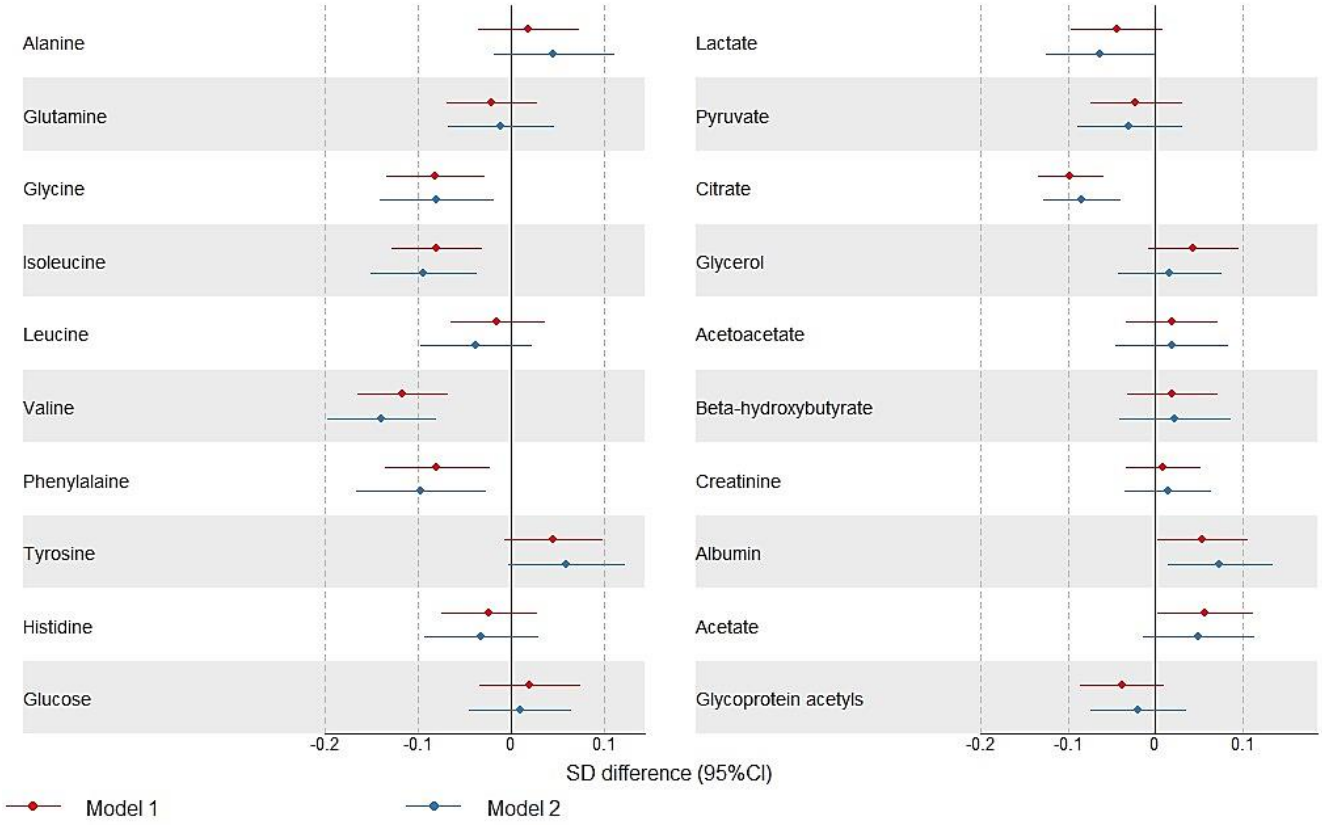


Figure 5-7. Cross-sectional associations between alcohol consumption and low-molecular-weight metabolites and hormonal measures.

All association were adjusted for age and sex in Model 1; and Model 1 plus region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 100 grams of alcohol per week. Association magnitudes in absolute concentration units are listed in Appendix Table 5-2 and continuous shapes of the metabolic associations with alcohol intake are shown in Appendix Figure 5-18 and Figure 5-19.

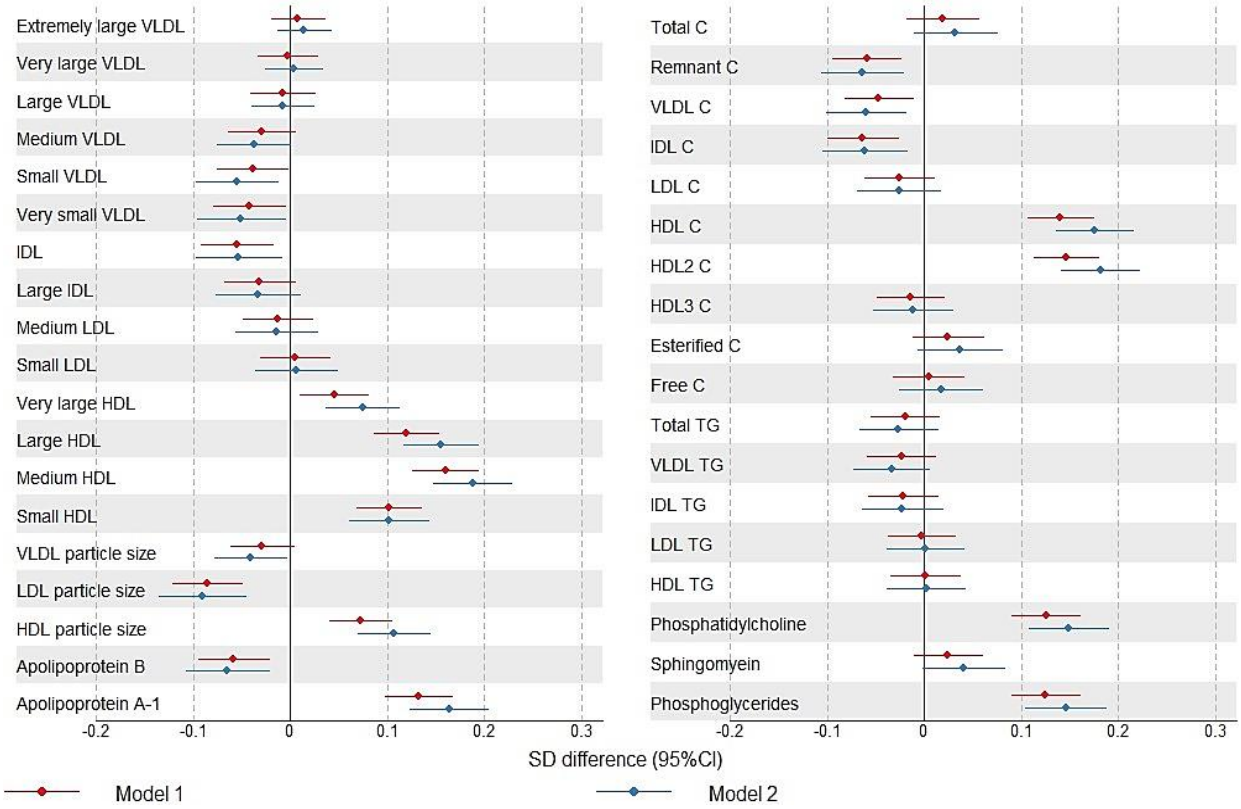


Figure 5-8. Cross-sectional associations between alcohol consumption and lipoprotein lipid measures.

All association were adjusted for age and sex in Model 1; and Model 1 plus region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 1 standard drink of alcohol per day

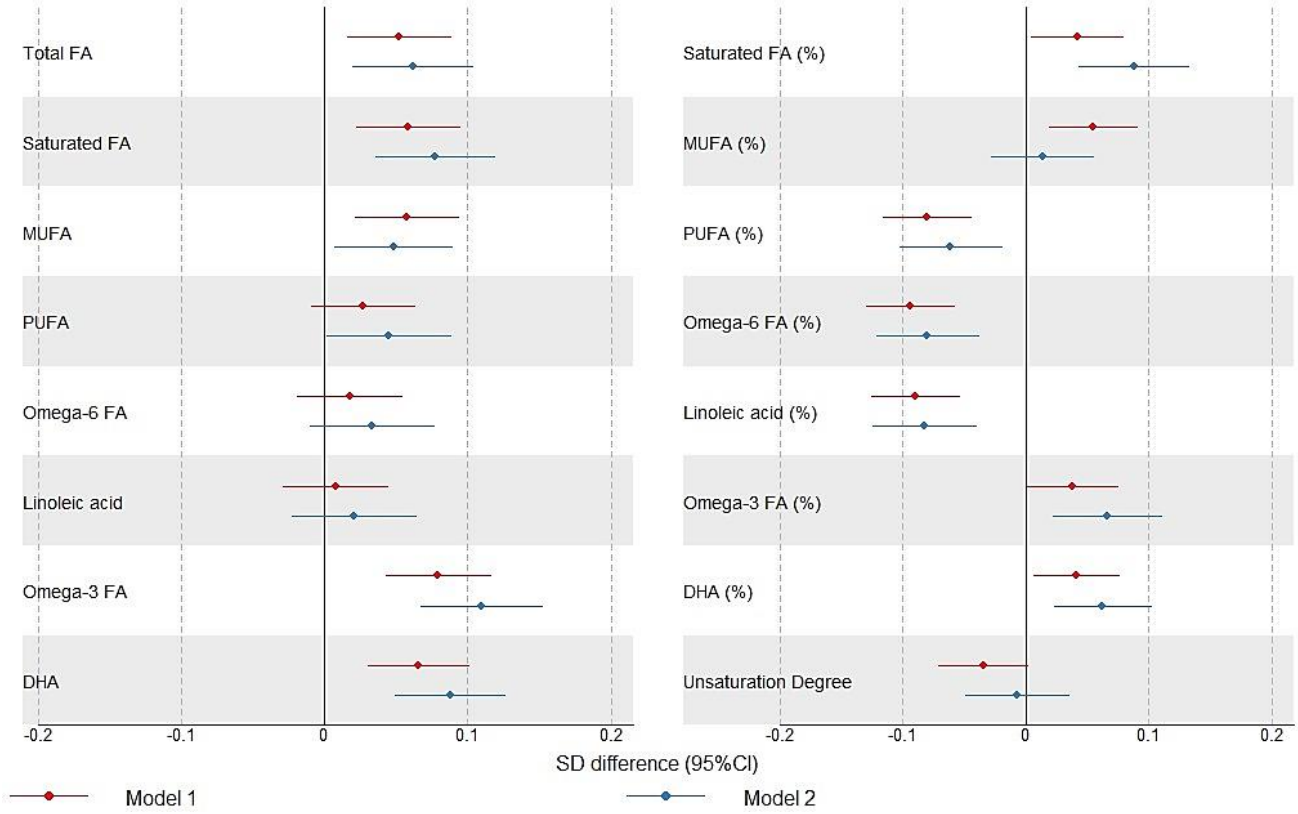


Figure 5-9. Cross-sectional associations between alcohol consumption and fatty acids.

All association were adjusted for age and sex in Model 1; and Model 1 plus region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 1 standard drink of alcohol per day

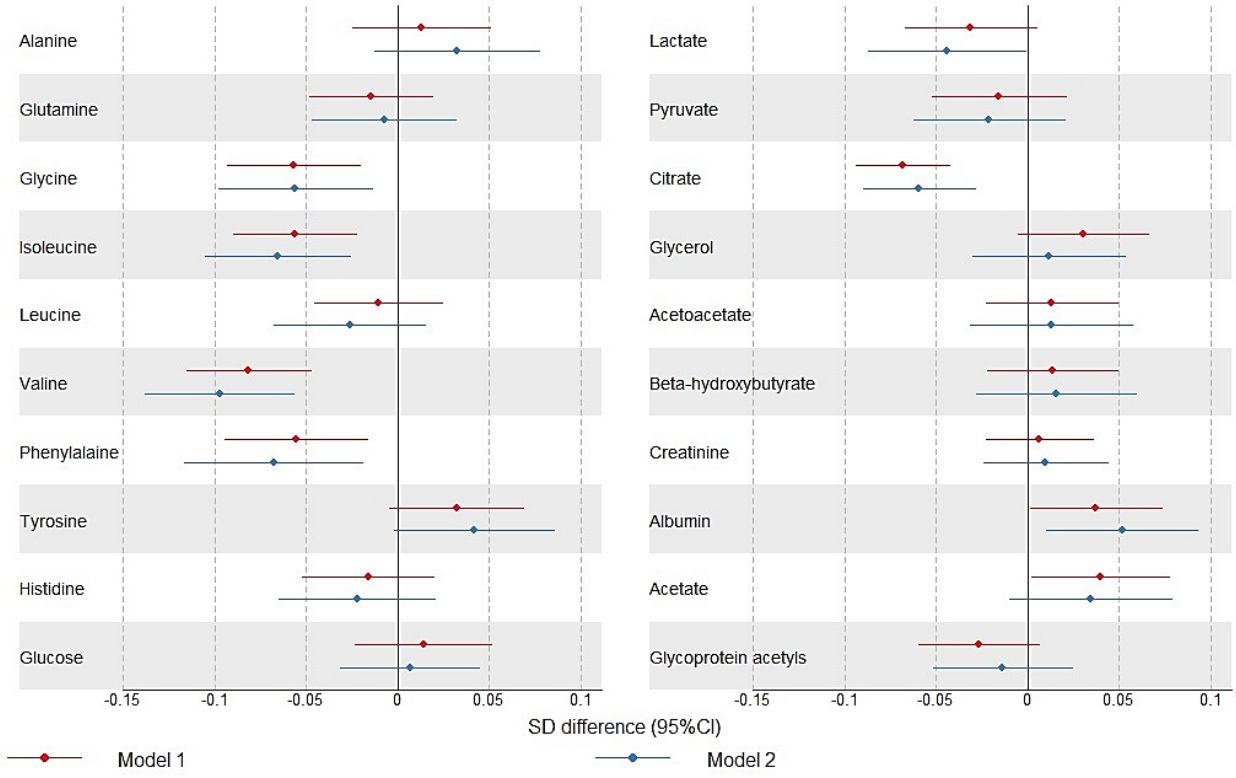


Figure 5-10. Cross-sectional associations between alcohol consumption and low-molecular-weight metabolites measures.

All association were adjusted for age and sex in Model 1; and Model 1 plus region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 1 standard drink of alcohol per day

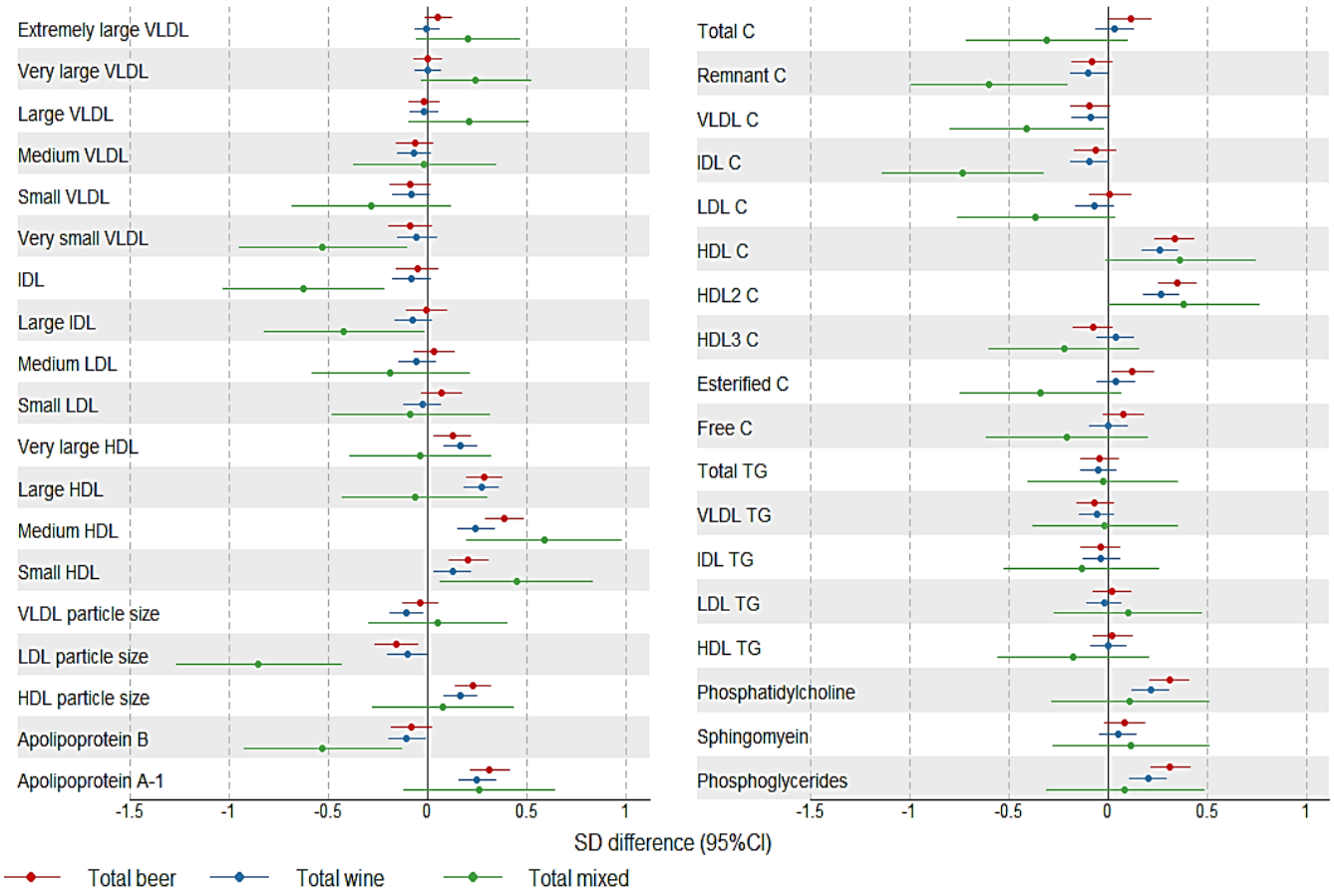


Figure 5-11. Cross-sectional associations between types of alcohol beverages and lipoprotein lipid measures.

All association were adjusted for sex, age, region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 100 grams of alcohol per week

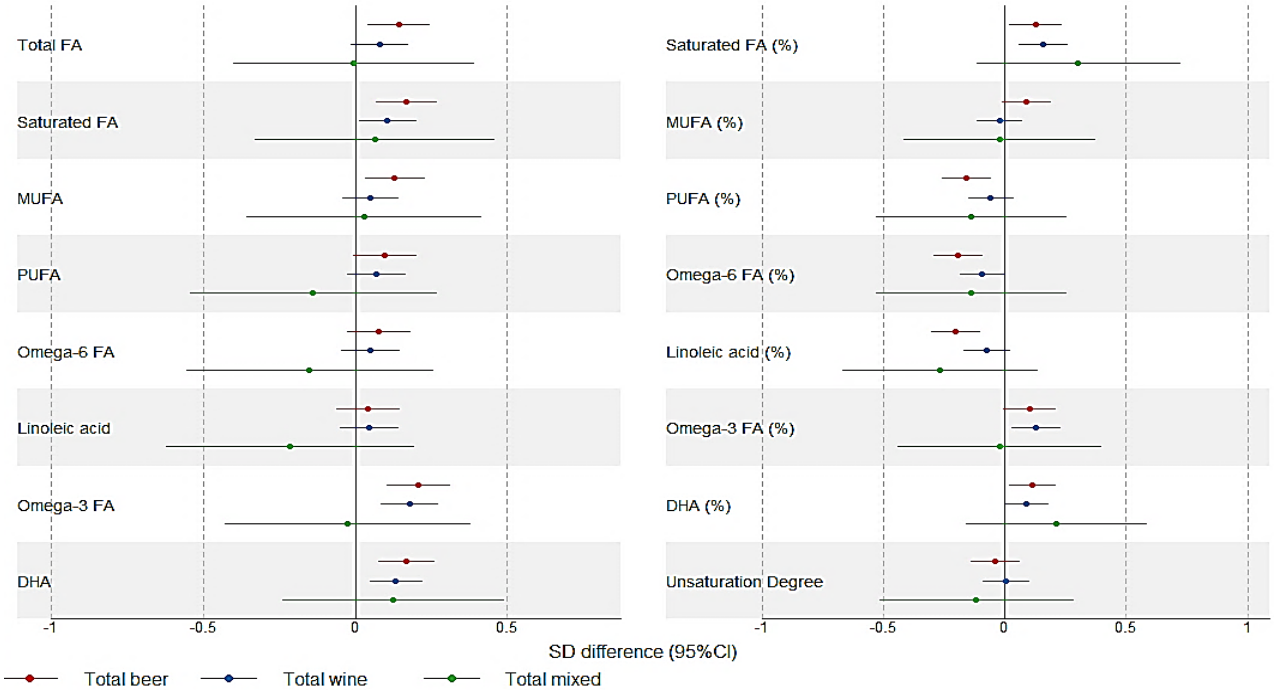


Figure 5-12. Cross-sectional associations between types of alcohol beverages and fatty acids.

All association were adjusted for sex, age, region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 100 grams of alcohol per week

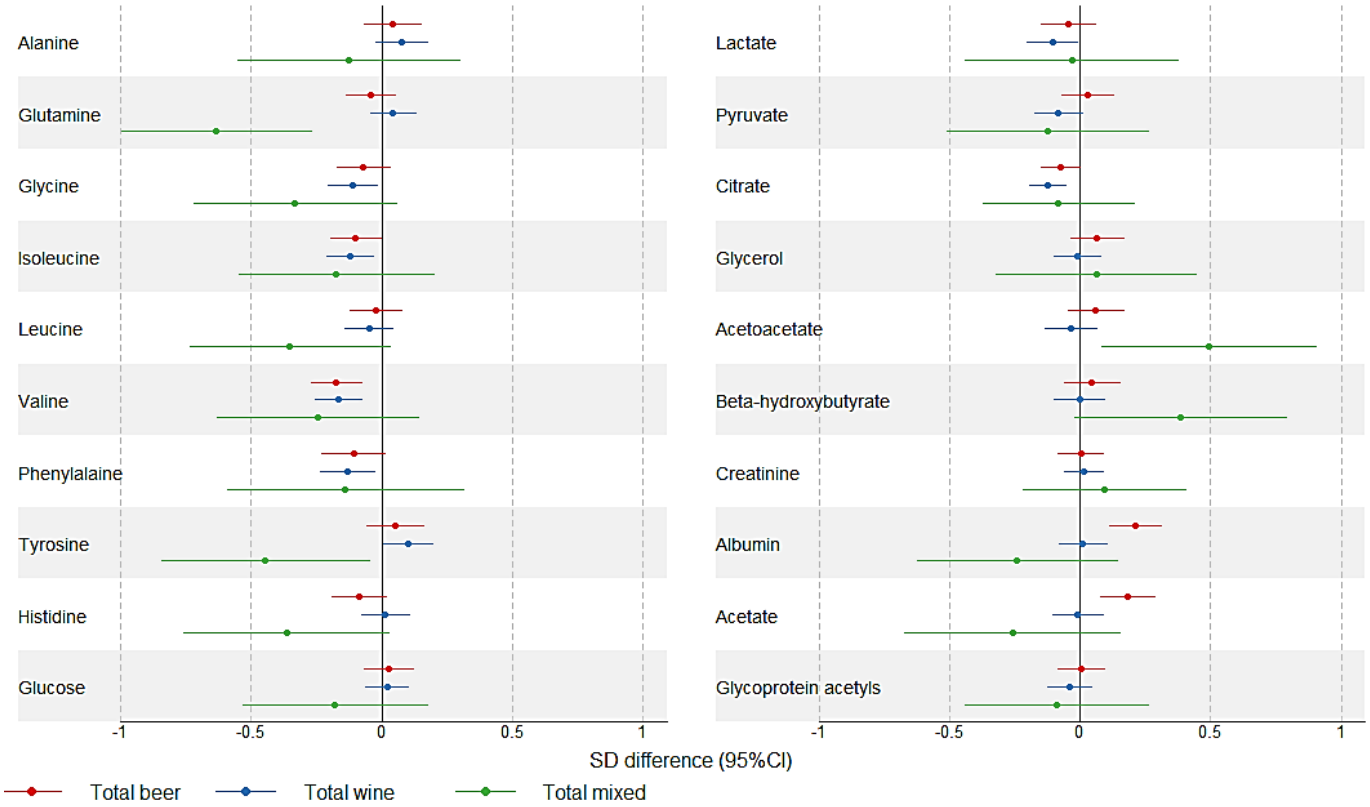


Figure 5-13. Cross-sectional associations between types of alcohol beverages and low-molecular-weight metabolites and measures.

All association were adjusted for sex, age, region of residence, SES status, educational level, occupation, marital status, smoking, diet quality, physical activity, cardiorespiratory fitness, depression and/or anxiety in Model 2. Error bars denote 95% confidence intervals. Differences in metabolite measures are expressed as standard deviation difference (95% CIs) in metabolite concentration per 100 grams of alcohol per week

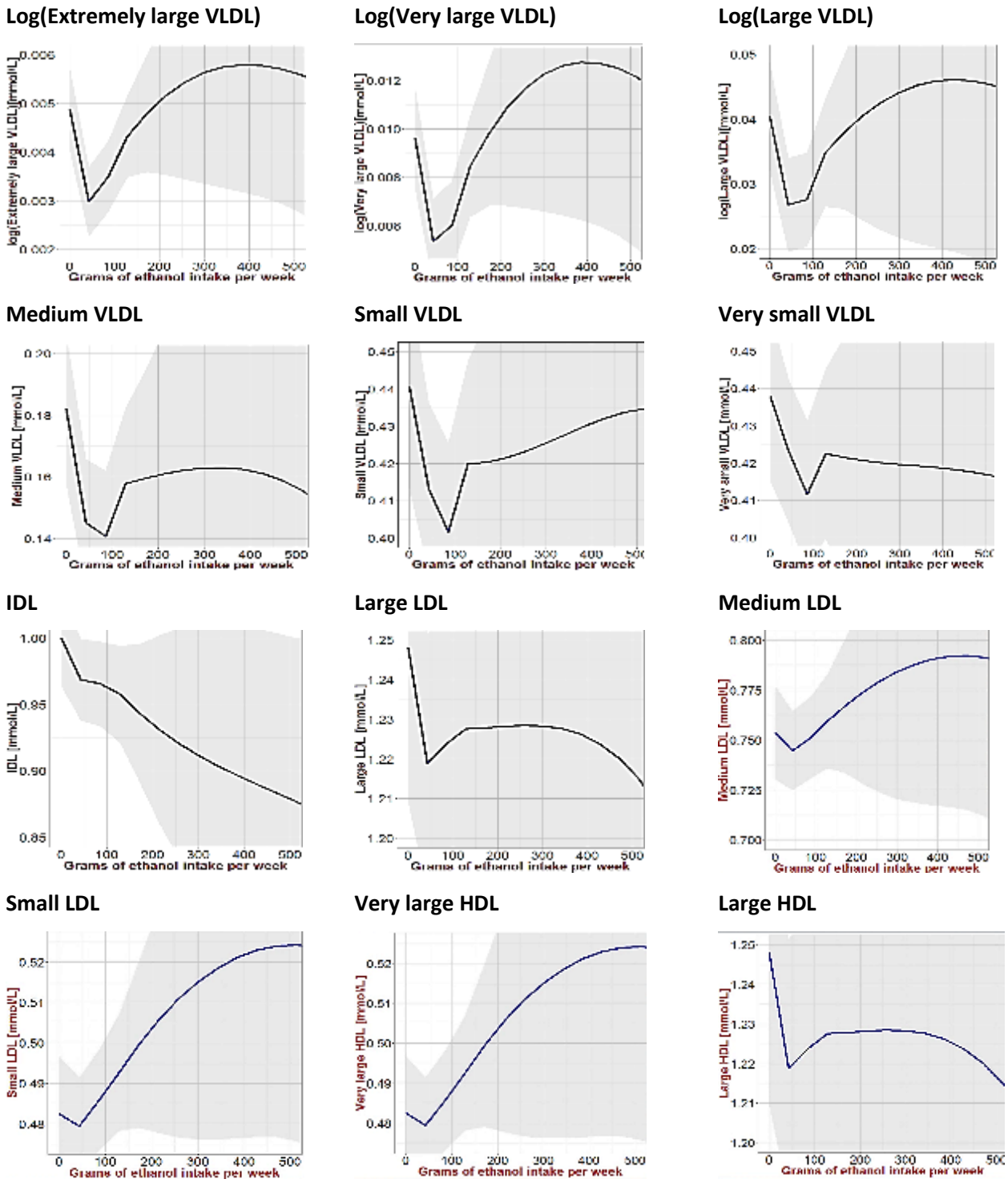


Figure 5-14. Continuous shape of the association between alcohol consumption and lipoprotein lipid measures (I).

The black curves denote the shape of the association, with the grey shaded area denoting the 95% confidence interval of the fit. The association shapes were derived using local quadratic regression fitting evaluated at 25 points

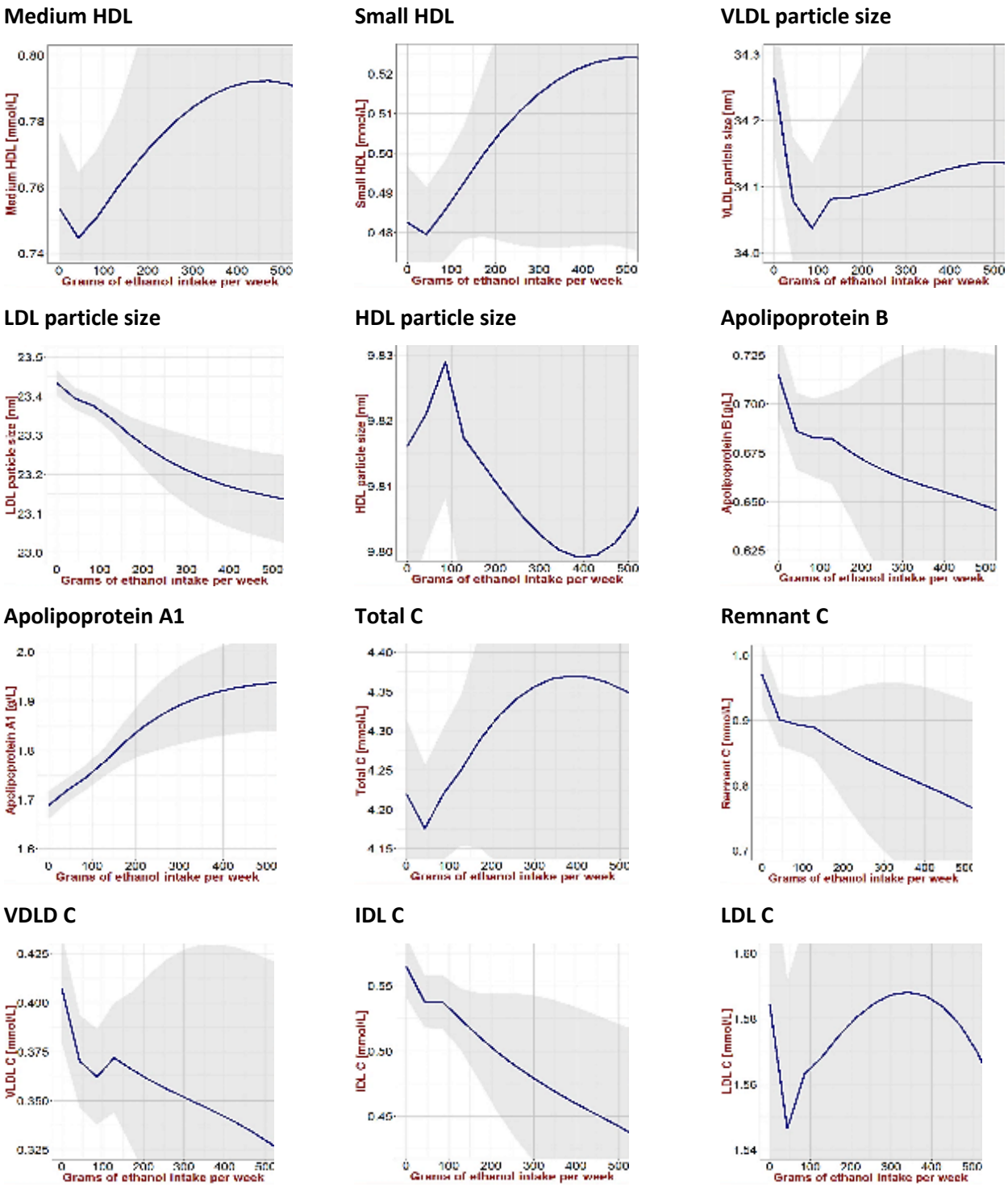
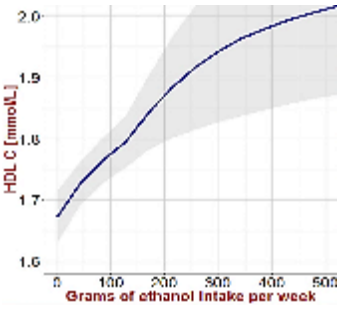


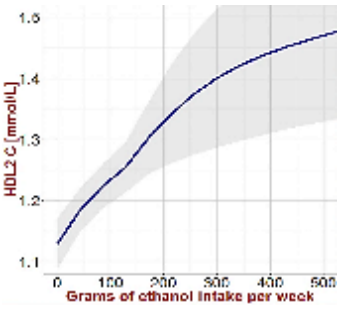
Figure 5-15. Continuous shape of the association between alcohol consumption and lipoprotein lipid measures (II).

The black curves denote the shape of the association, with the grey shaded area denoting the 95% confidence interval of the fit. The association shapes were derived using local quadratic regression fitting evaluated at 25 points

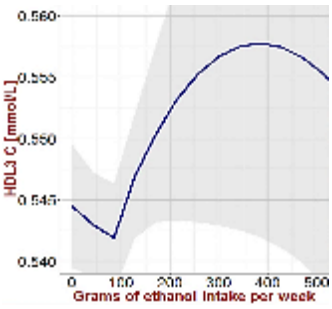
HDL C



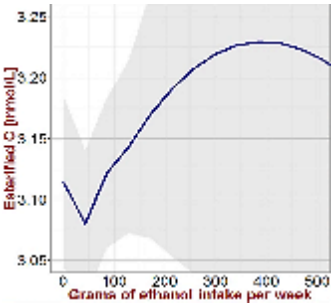
HDL2 C



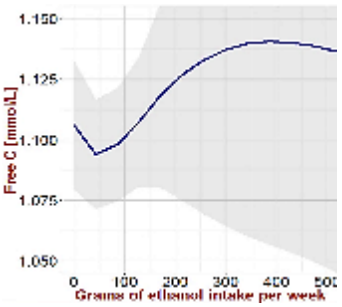
HDL 3 C



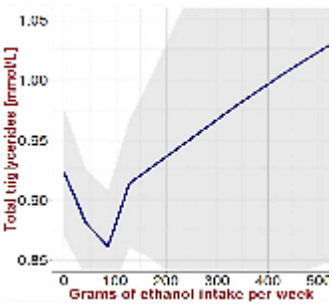
Esterified C



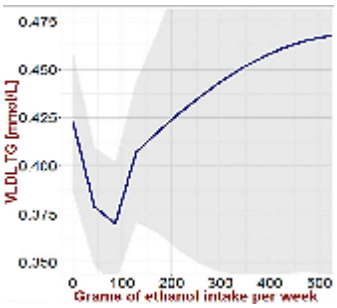
Free C



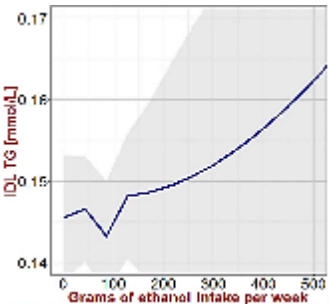
Total triglycerides



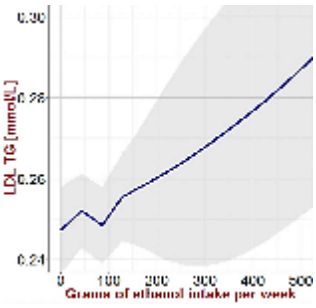
VLDL TG



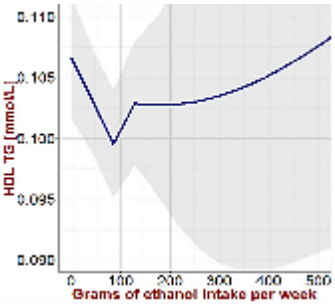
IDL TG



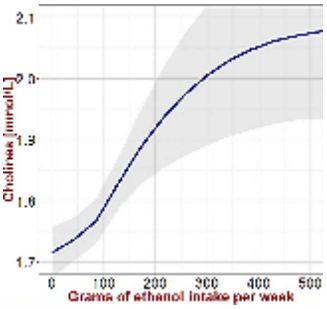
LDL TG



HDL TG



Cholines



Phosphoglycerides

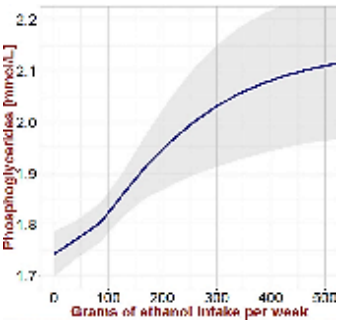
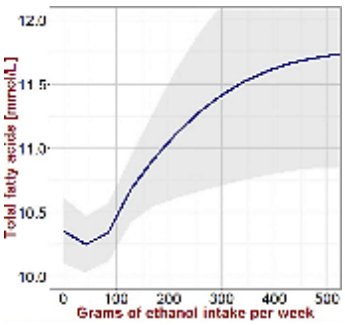
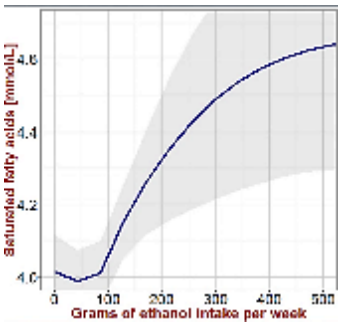


Figure 5-16. Continuous shape of the association between alcohol consumption and lipoprotein lipid measures (III).

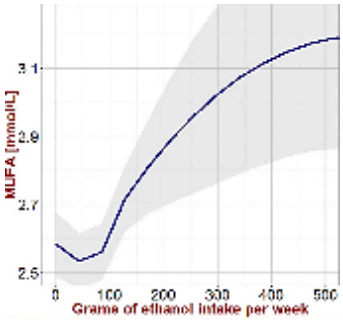
Total fatty acids



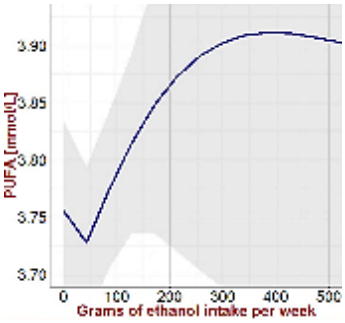
Saturated fatty acids



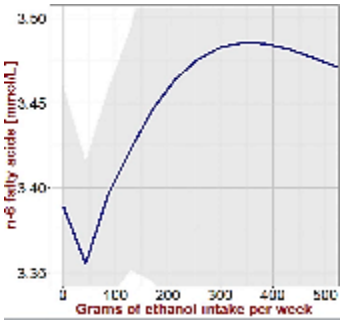
MUFA



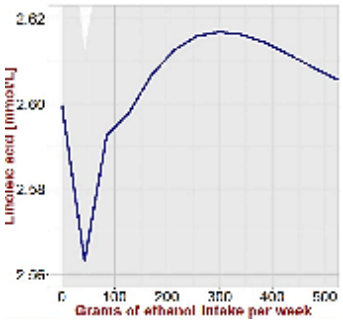
PUFA



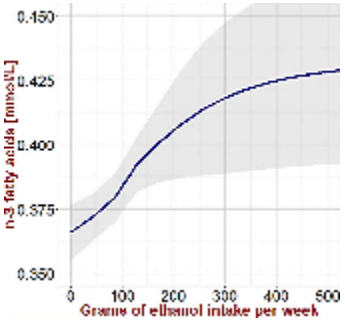
Omega-6 fatty acids



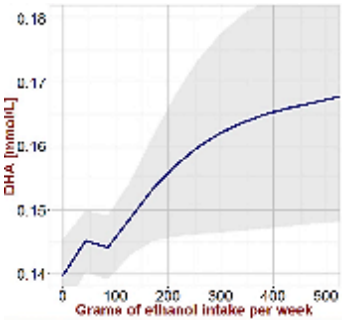
Linoleic acid



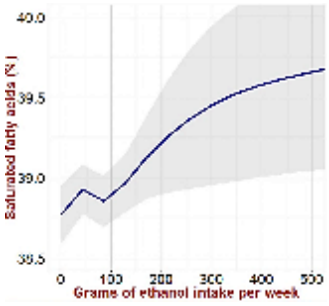
Omega-3 fatty acids



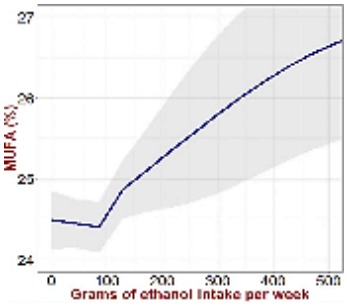
DHA



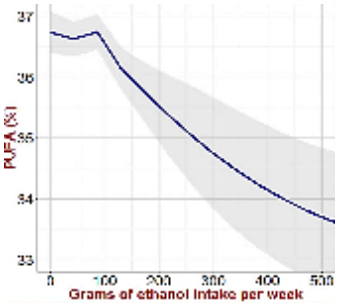
Saturated fatty acids (%)



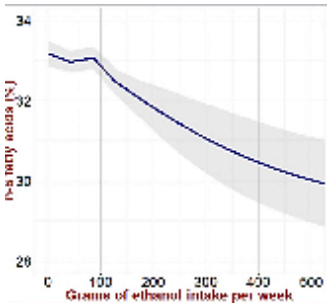
MUFA (%)



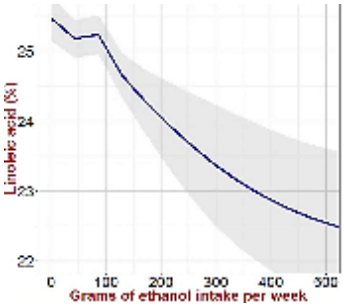
PUFA (%)



Omega-6 fatty acids (%)



Linoleic acid (%)



Omega-3 fatty acids (%)

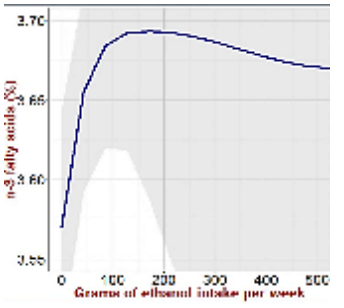


Figure 5-17. Continuous shape of the association between alcohol consumption and fatty acids.

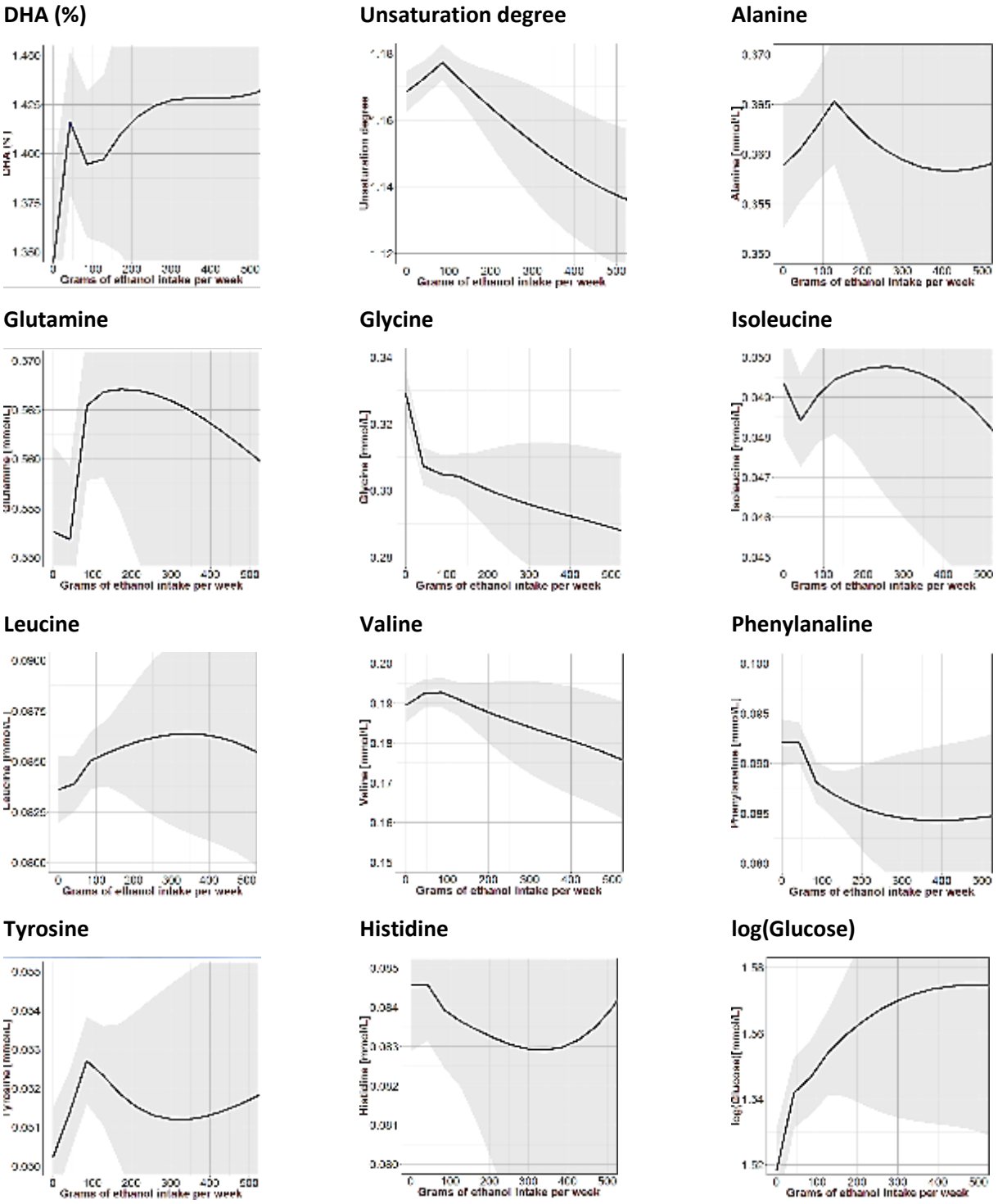
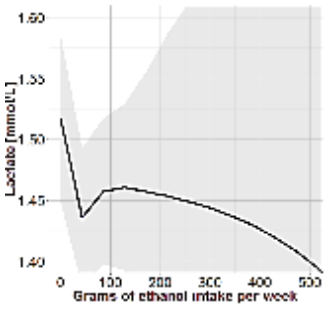
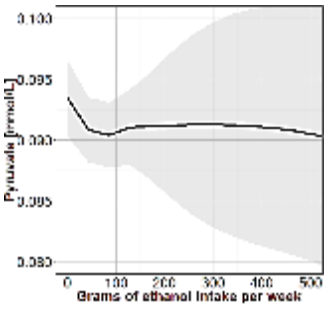


Figure 5-18. Continuous shape of the association between alcohol consumption and low-molecular-weight metabolites and hormonal measures (I).

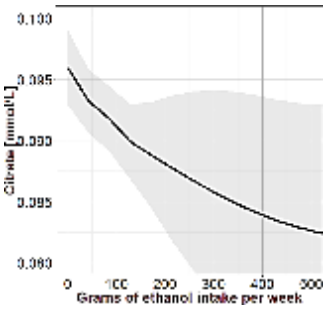
Lactate



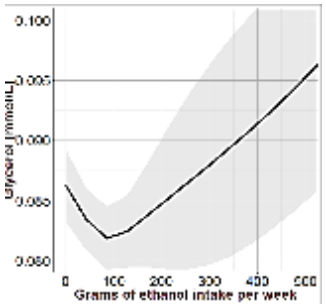
Pyruvate



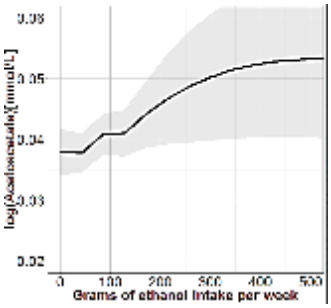
Citrate



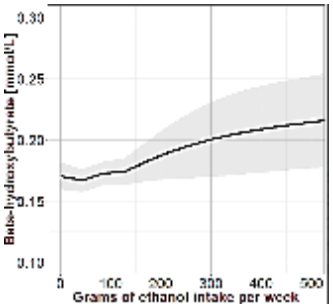
Glycerol



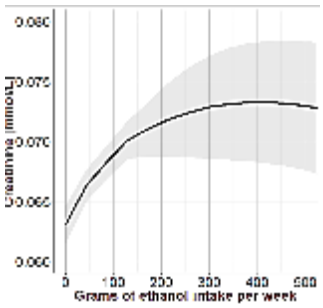
log(Acetoacetate)



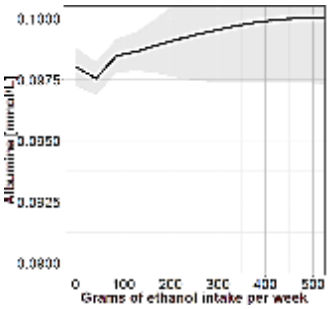
Beta-hydroxybutyrate



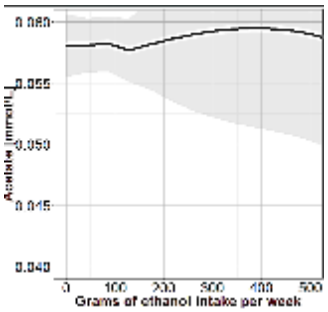
Creatinine



Albumine



Acetate



Glycoprotein acetyls

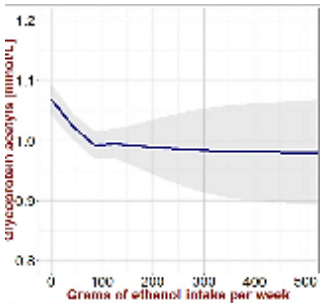


Figure 5-19. Continuous shape of the association between alcohol consumption and low-molecular-weight metabolites and hormonal measures (II).

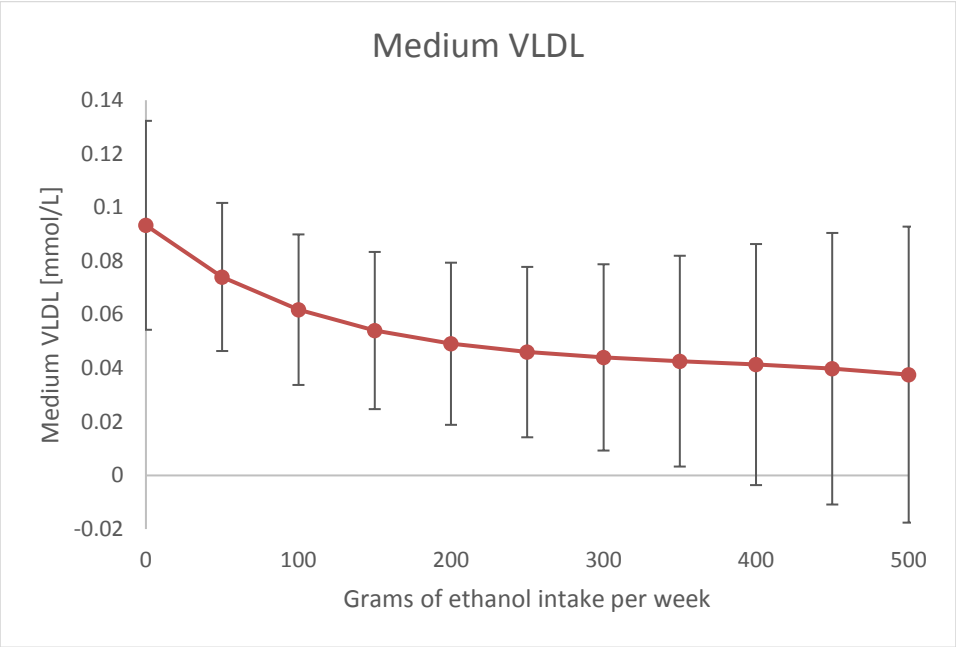


Figure 5-20. Continuous shape of the non-linear associations between alcohol consumption and medium very-low-density lipoprotein

Association magnitudes in absolute concentration units are listed in Appendix Table 5-3.

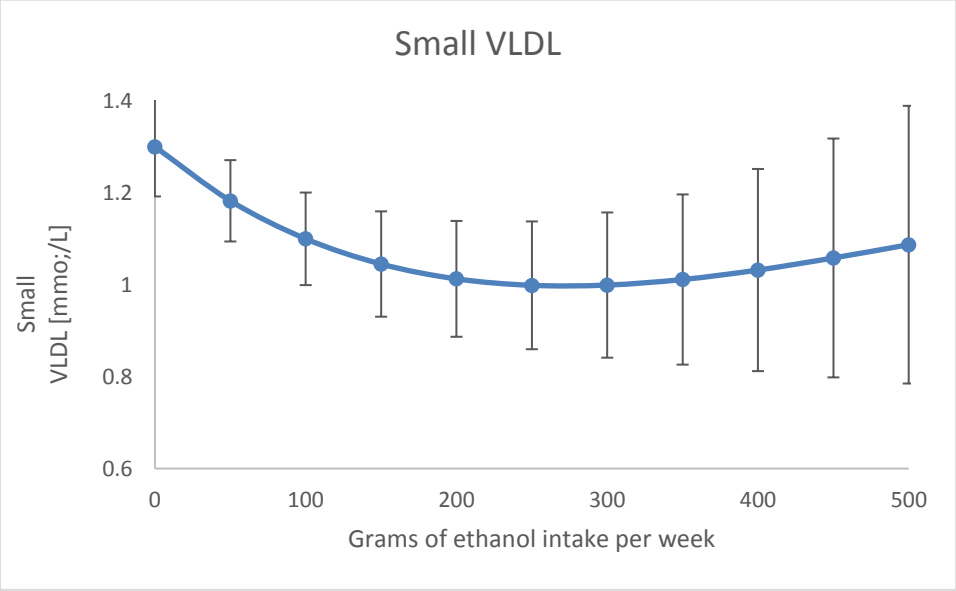


Figure 5-21. Continuous shape of the non-linear associations between alcohol consumption and small very-low-density lipoprotein

Association magnitudes in absolute concentration units are listed in Appendix Table 5-3.

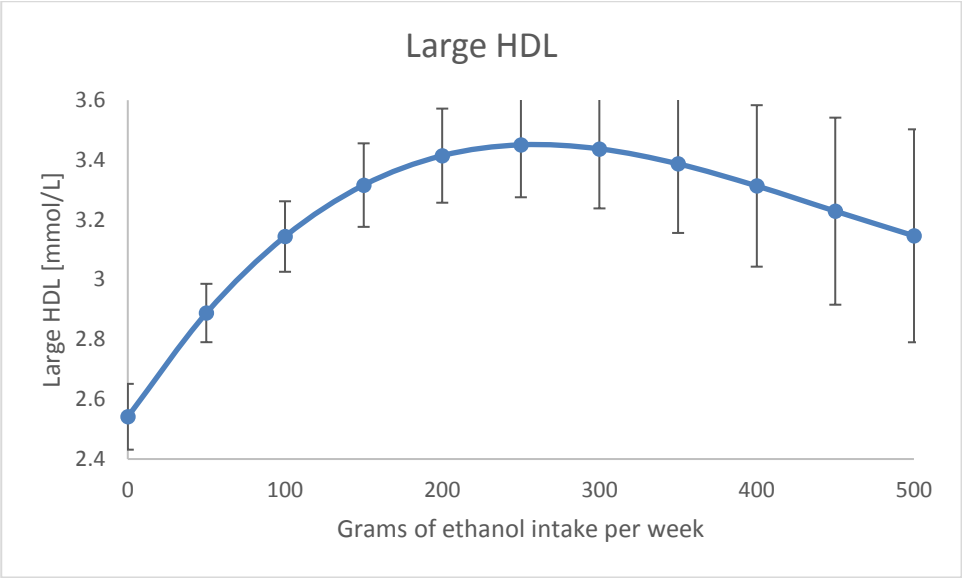


Figure 5-22. Continuous shape of the non-linear associations between alcohol consumption and large high-density lipoprotein

Association magnitudes in absolute concentration units are listed in Appendix Table 5-3.

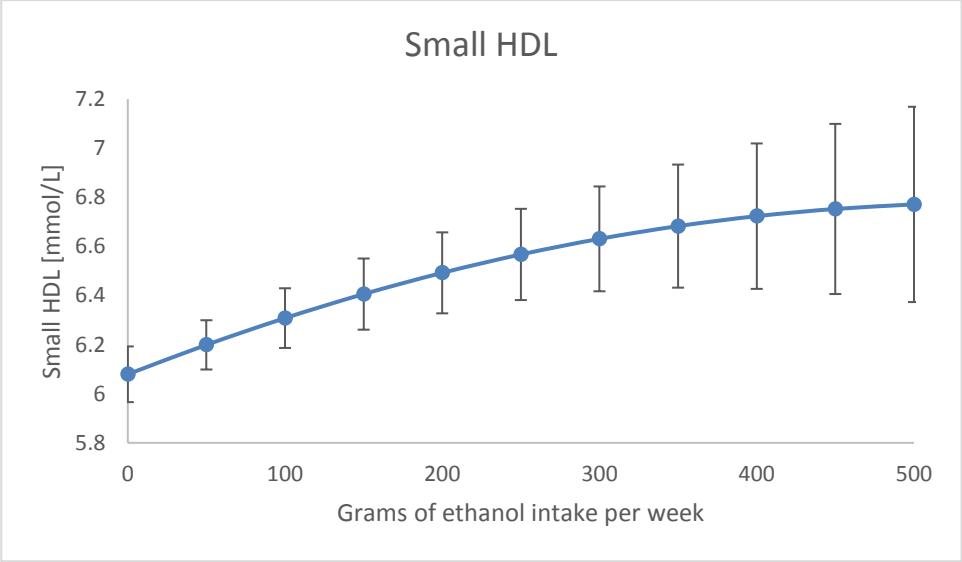


Figure 5-23. Continuous shape of the non-linear associations between alcohol consumption and small high-density lipoprotein

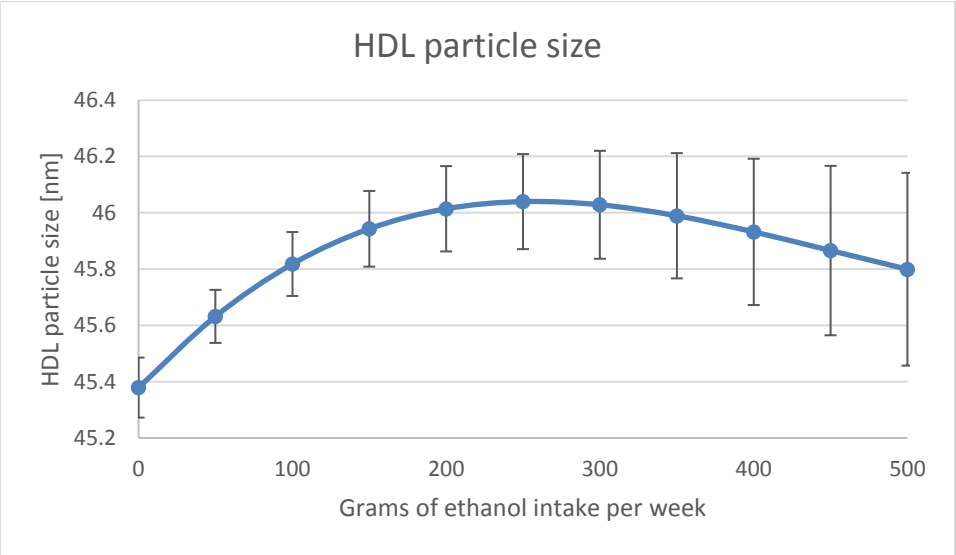


Figure 5-24. Continuous shape of the non-linear associations between alcohol consumption and high-density lipoprotein particle size

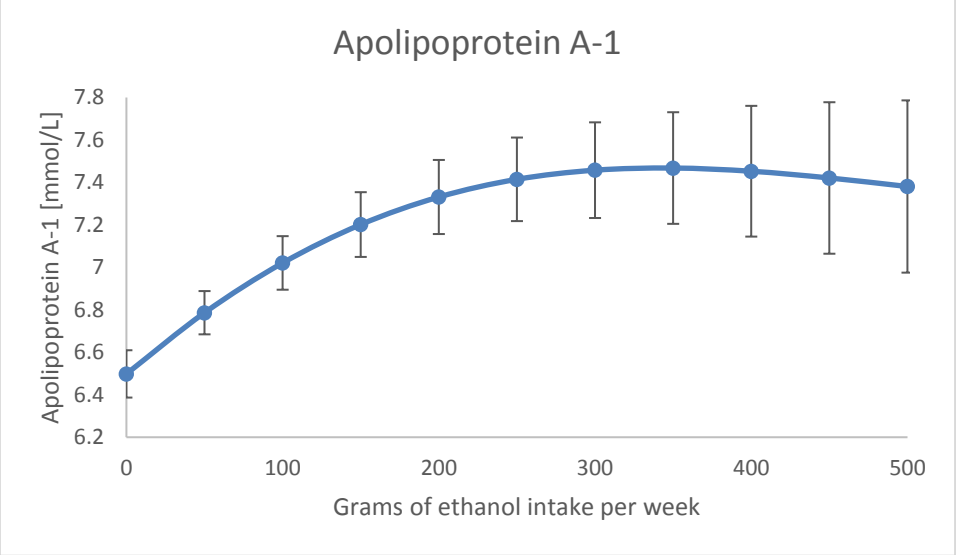


Figure 5-25. Continuous shape of the non-linear associations between alcohol consumption and apolipoprotein A-1

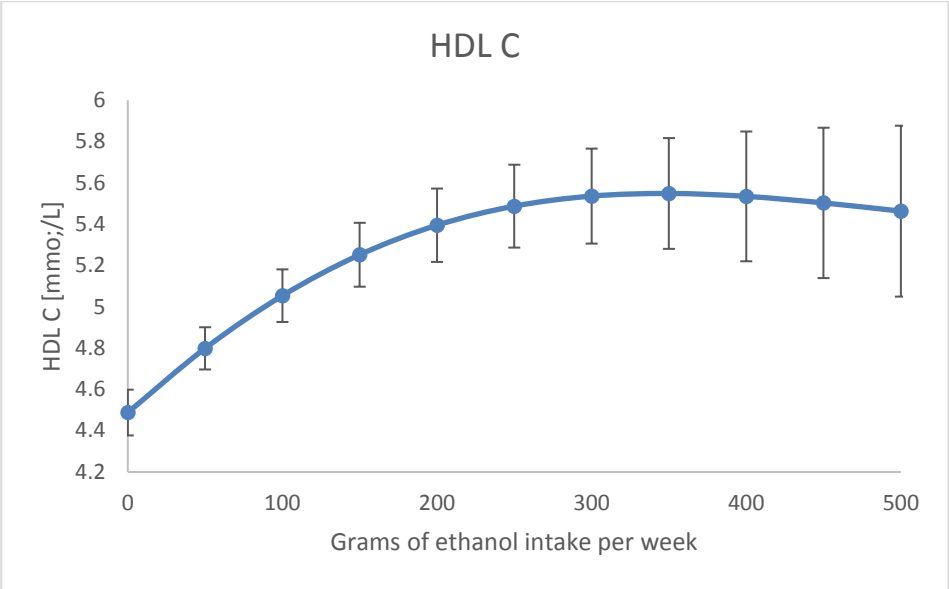


Figure 5-26. Continuous shape of the non-linear associations between alcohol consumption and high-density lipoprotein cholesterol

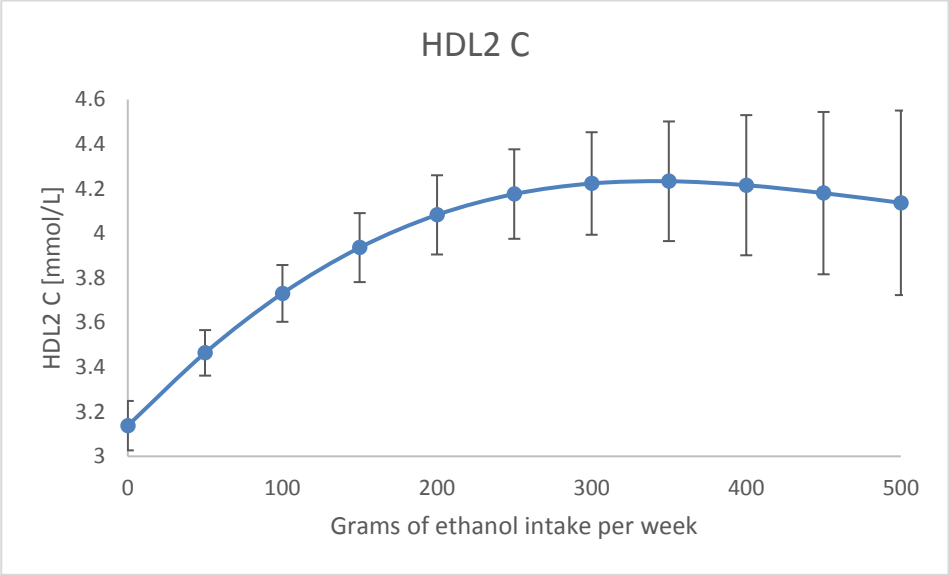


Figure 5-27. Continuous shape of the non-linear associations between alcohol consumption and high-density lipoprotein cholesterol - 2

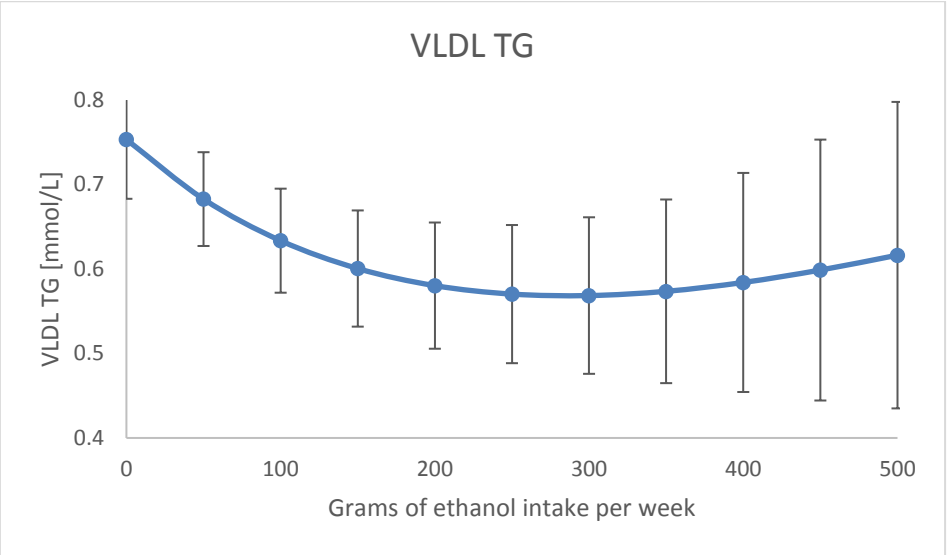


Figure 5-28. Continuous shape of the non-linear associations between alcohol consumption and very-low-density lipoprotein triglycerides

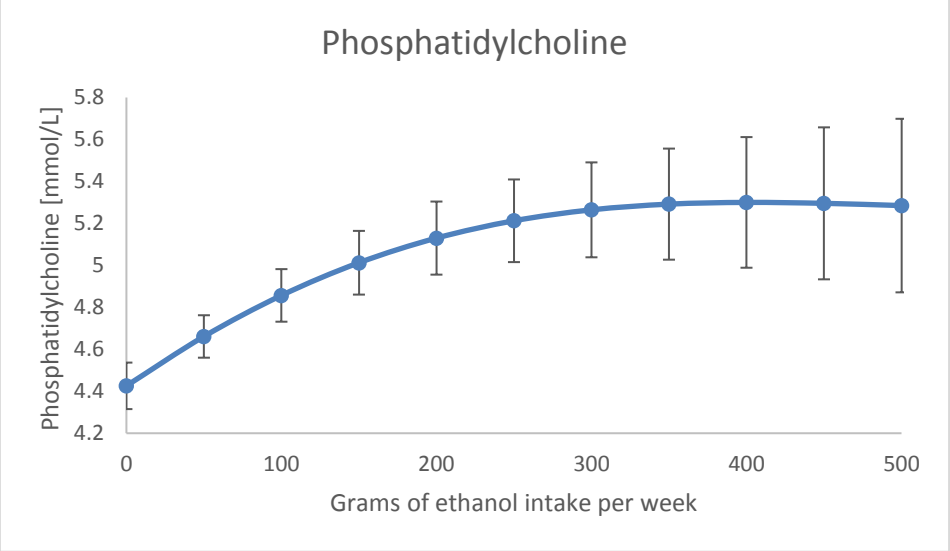


Figure 5-29. Continuous shape of the non-linear associations between alcohol consumption and phosphatidylcholine

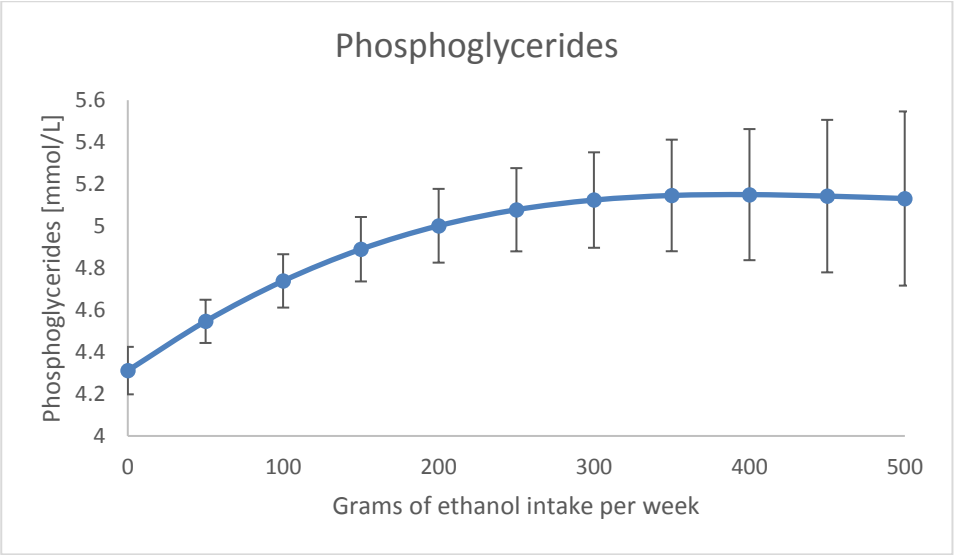


Figure 5-30. Continuous shape of the non-linear associations between alcohol consumption and phosphoglycerides

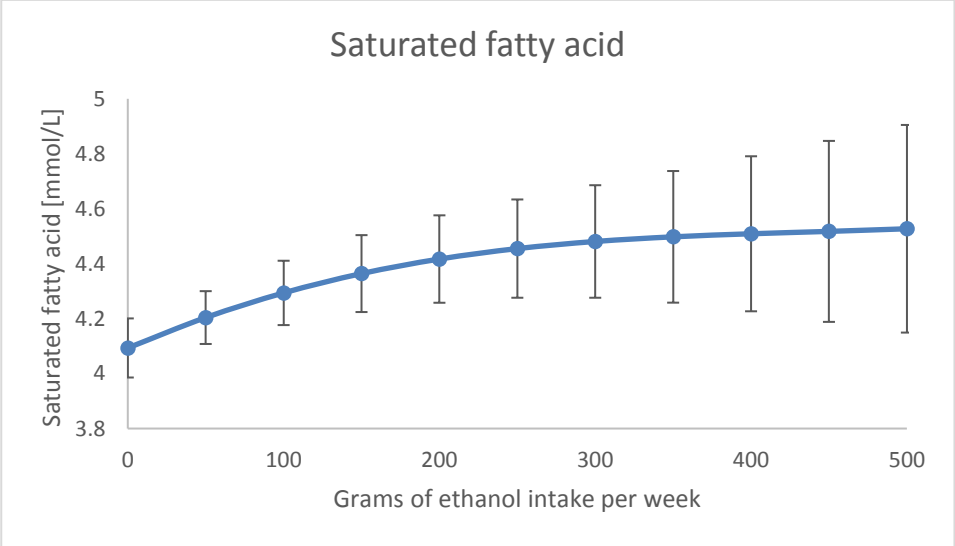


Figure 5-31. Continuous shape of the non-linear associations between alcohol consumption and saturated fatty acid

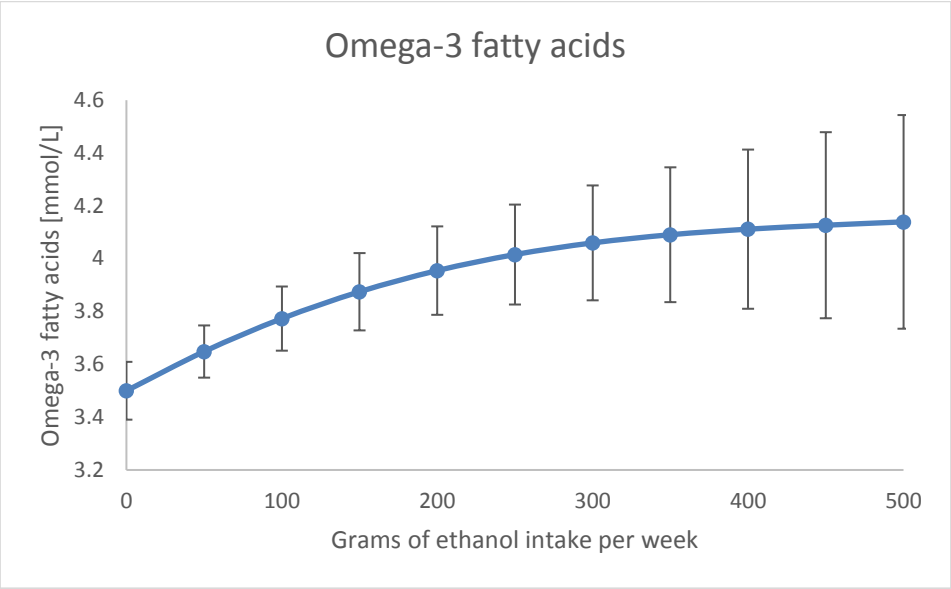


Figure 5-32. Continuous shape of the non-linear associations between alcohol consumption and omega-3 fatty acid

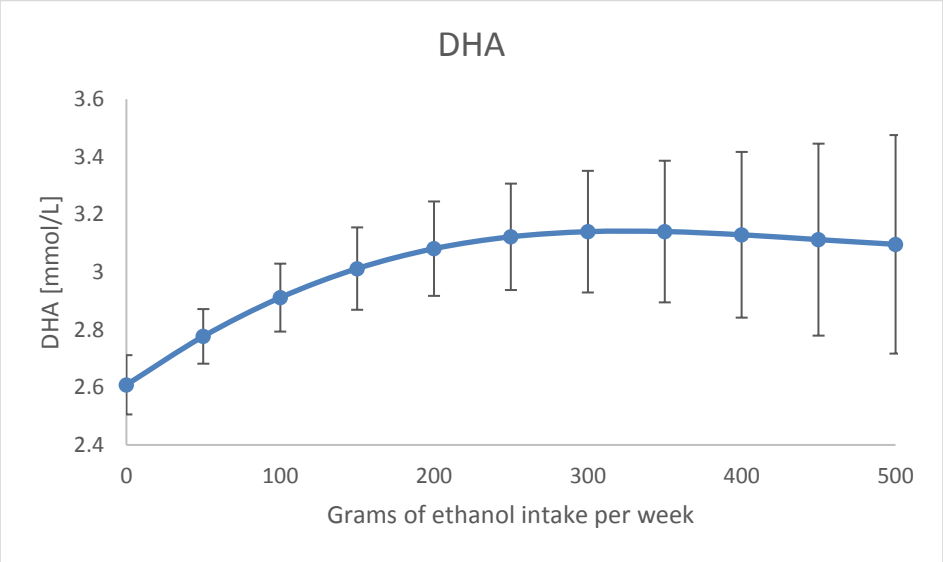


Figure 5-33. Continuous shape of the non-linear associations between alcohol consumption and docosahexaenoic acid

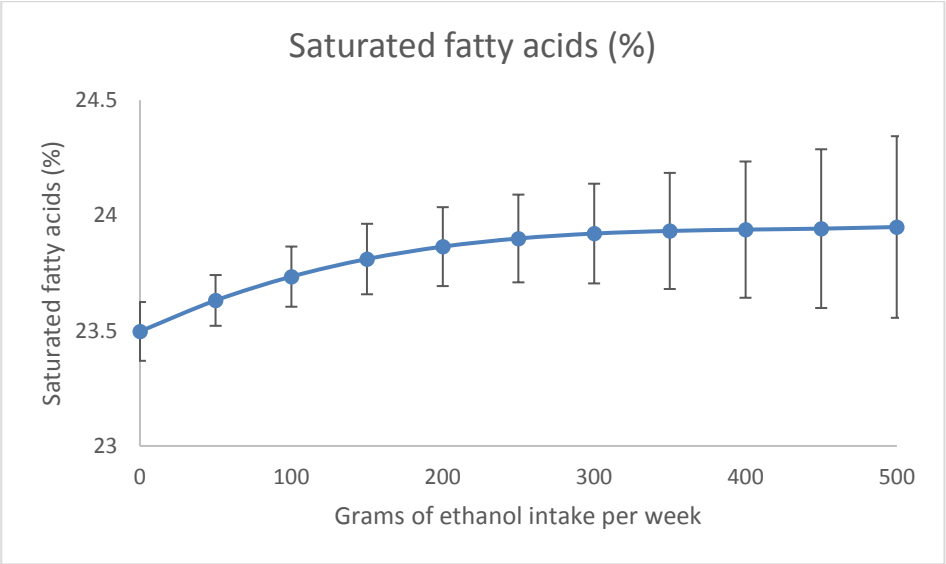


Figure 5-34. Continuous shape of the non-linear associations between alcohol consumption and saturated fatty acids

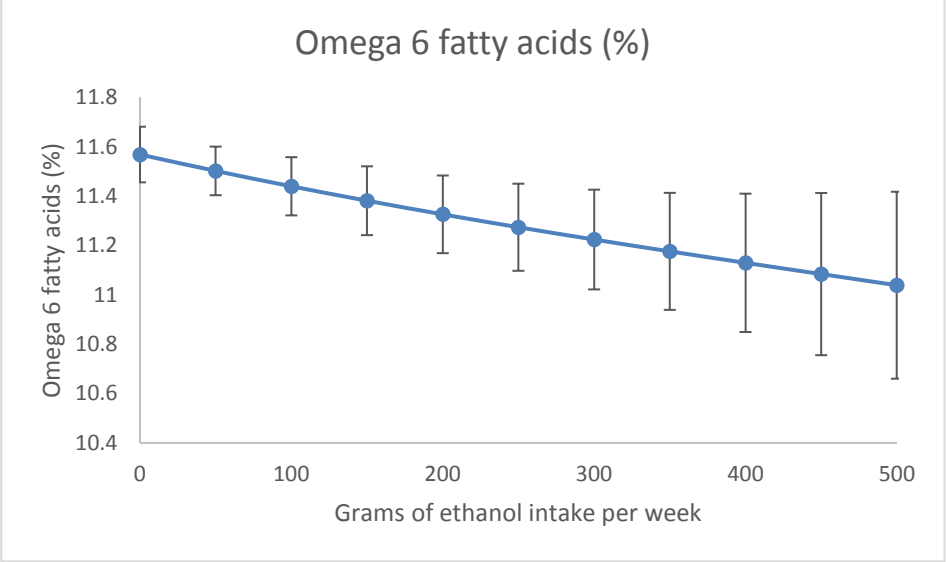


Figure 5-35. Continuous shape of the non-linear associations between alcohol consumption and omega-6 fatty acids

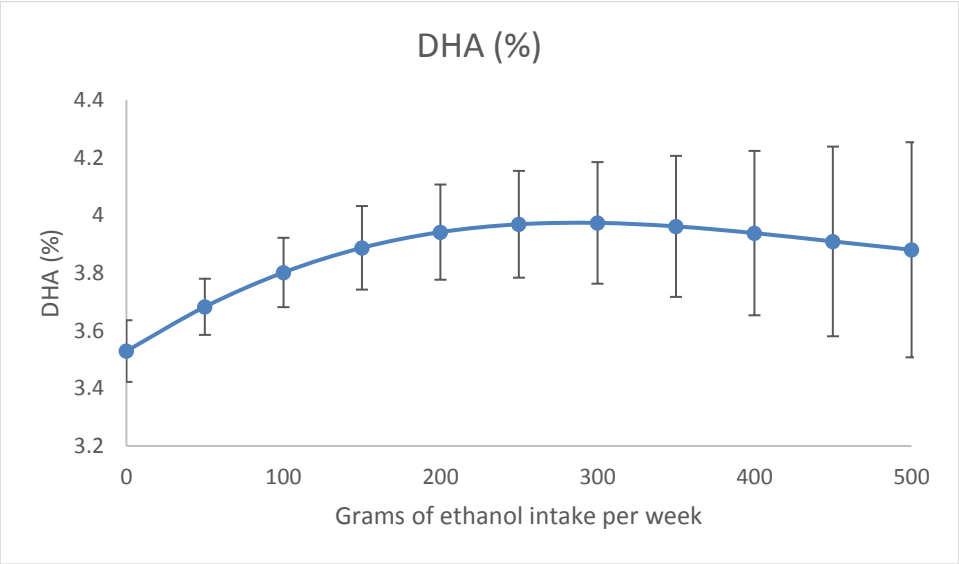


Figure 5-36. Continuous shape of the non-linear associations between alcohol consumption and the proportion of docosahexaenoic acid to total fatty acid

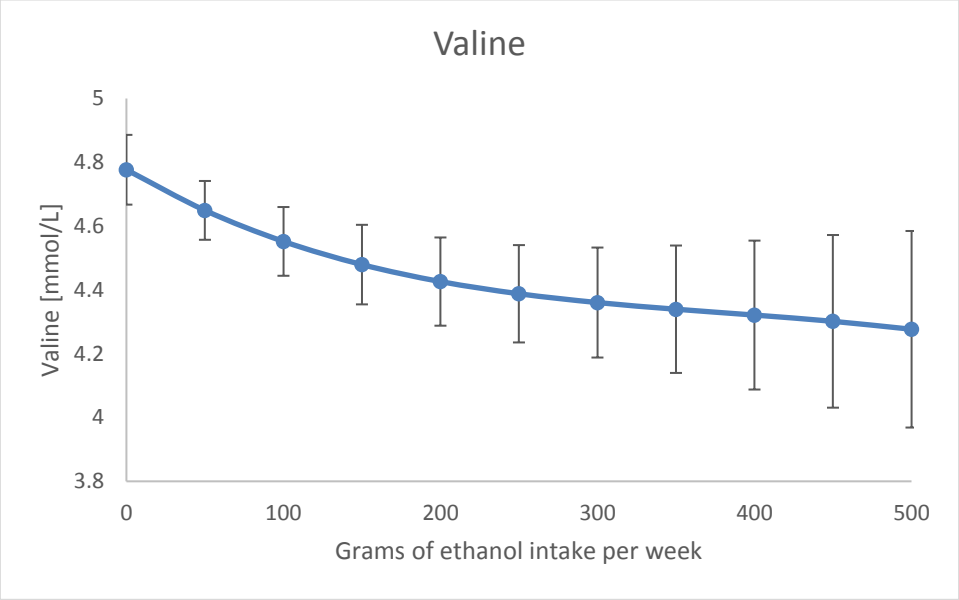


Figure 5-37. Continuous shape of the non-linear associations between alcohol consumption and valine

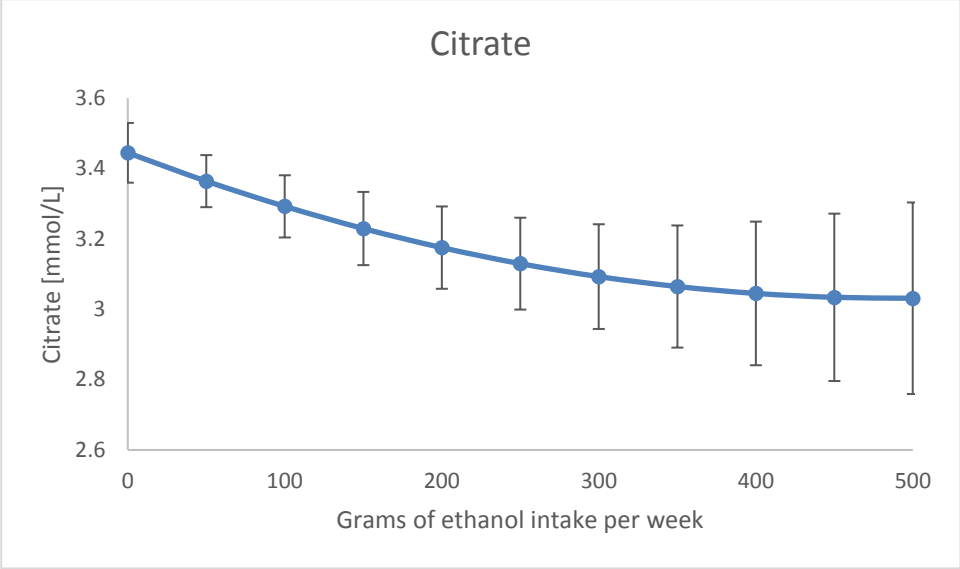


Figure 5-38. Continuous shape of the non-linear associations between alcohol consumption and citrate

Chapter 6

An examination of bidirectional associations between physical activity and alcohol consumption in adulthood: A 5-year cohort study

6 Chapter 6. An examination of bidirectional associations between physical activity and alcohol consumption in adulthood: A 5-year cohort study

6.1. Introduction

There has been recent recognition of the inter-relationships between physical activity and alcohol consumption and how these factors may jointly modify the risk of disease [76, 77]. Physical activity provides a wealth of benefits to health, protecting against a range of diseases. In contrast, alcohol consumption is not typically regarded as a health-promoting behaviour and there is ongoing debate about the benefits of moderate alcohol intake, compared to abstainers or heavy drinkers, in relation to risk of CVD [79-81]. Health behaviours tend to cluster together and research on the health behaviours of moderate drinkers has identified a positive association with physical activity, as well as better diet quality, compared to people that do not drink or drink excessively [273]. Understanding the inter-relationship between alcohol consumption and other health behaviours may help us to understand the recent findings refuting the benefits of moderate alcohol consumption for health [80, 117].

There is a small body of literature examining the associations between alcohol consumption and physical activity; however, most studies have been cross-sectional with less than ideal measurements of physical activity. In general, findings from these studies have suggested a positive linear association between physical activity and alcohol in the general population [82, 83]. Results were consistent across groups of athletes or people doing organised sports [274, 275], or among adolescents [276, 277]. The studies have tended to be cross-sectional [82, 83, 274, 275], thereby preventing examination of any temporal sequence between alcohol consumption and physical activity. The few longitudinal studies that have examined this association have mostly assessed physical activity at a single time point predicting alcohol consumption at a single later time point. These studies have shown that people that engage in more physical activity drink more [276] or less [277] than those that do less physical activity. This assumes that physical activity and alcohol consumption remain stable over time. There has also not been examination of whether alcohol consumption predicts

physical activity [276, 277]. This is potentially important for understanding ways to promote physical activity as alcohol consumption may be a barrier or facilitator to this behaviour.

The mechanisms by which alcohol consumption and physical activity are related to each other are poorly understood. Previous authors have suggested that it is not a direct relationship but rather indirect through shared social and cognitive factors, as discussed in the previous chapter. This may include socioeconomic factors, personality and motivation. Few studies have been able to control for a wide range of potential explanatory factors to increase our understanding of how these two important health behaviours relate to each other.

The period from younger to middle adulthood may be particularly important for alcohol consumption [278]. Population level data from Australia suggest that people in their 40s years are those most likely to drink at risky levels [47]. This period also coincides with many life stage transition such as getting married and having children that have been shown to influence other health behaviours and outcomes such as smoking [279] and physical activity [280]. There are relatively few studies of changes in alcohol consumption among general populations during this period of life [281, 282]. Studying this age group may be important for understanding how to target potential public health messages related to alcohol consumption in this group.

In the present study, we used measures of physical activity and alcohol consumption during 5 years of follow-up in a longitudinal Australian cohort of young adults to investigate the potential bidirectional associations between physical activity and alcohol consumption.

6.2. Methods

6.2.1. Study population

The present study was part of the CDAH study, which was a prospective cohort study. The study began in 1985 as the ASHFS with a representative sample of 8,498 children aged 7–15 years. Sampling procedures and methods of data collection are presented elsewhere [235]. In brief, in 2004–2006 (herein ‘baseline’), when participants were 26–36 years old, they completed assessments of their lifestyle, including physical activity and alcohol consumption (n = 2,031). In 2009–2011 (herein ‘follow-up’), when participants were 31–41 years old, (n = 1,322) completed repeated assessments of alcohol consumption and physical activity.

6.2.2. Measures

6.2.2.1.Physical activity

Physical activity was assessed using two methods at baseline and follow-up. The long version of the self-reported International Physical Activity Questionnaire (IPAQ) was administered. Participants were asked questions such as how many days in a typical week they spent in light, moderate (e.g. carrying light loads and cycling) and vigorous (e.g. fast cycling, aerobics and heavy lifting) physical activity for transportation, household tasks, work and leisure time. For each of the categories of physical activity engaged in at least once per week, participants were asked to provide information on the duration spent in that activity on a typical day. To derive time spent in moderate to vigorous physical activity, the activity frequency was multiplied by the duration spent in the activity. Participants also wore pedometers (Yamax Digiwalker SW-200; Yamax USA, San Antonio, TX) during waking hours for seven consecutive days to objectively measure ambulatory activity. For analysis, the average number of steps per day was calculated from participants with four or more measurement days.

6.2.2.2.Alcohol consumption

We collected information about alcohol consumption from a FFQ at the baseline and follow-up. Frequency of intake (options: never or <1/month, 1–3 times/month, once/week, 2–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–5 times/day and >6 times/day) of alcoholic beverages (options: light, medium or full strength beer; red, white and sparkling wine; wine cooler; spirits/liqueurs; spirit-based mixed drinks; sherry/port and other) over the last 12 months was reported. We assumed that one standard drink (10 g of alcohol) was consumed at each drinking occasion. We estimated alcohol consumed per day for each beverage type by multiplying the frequency of drinking by the estimated grams of alcohol for each beverage type. Total amount of alcohol consumed per day was defined as the sum of the amount of alcohol consumed for each type of beverage [174]. Self-reported alcohol intake by FFQ has been shown to be a reliable and valid instrument in young adults [16].

6.2.3. Statistical analysis

6.2.3.1. Physical activity and daily steps at baseline predicting changes in alcohol consumption between baseline and follow-up

We used multivariable linear regression models to examine whether physical activity (total, leisure time, work-related, home-related and intensity of physical activity) and daily steps at the baseline predicted changes in alcohol consumption during follow-up (calculated as Total alcohol consumption [g/day] follow-up – Total alcohol consumption [g/day] baseline). Log multinomial regression was used to estimate the relative risk (RR ± 95% CI) of changing category of alcohol consumption over follow-up by physical activity and daily steps at baseline. Total alcohol consumption at baseline and follow-up were categorised as non-drinkers (0 g/day), light drinkers (>0–10 g/day), moderate drinkers (>10–20 g/day) and heavy drinkers (>20 g/day) based on Australian guidelines [13]. Categorical change variables were created as follows: persistently low (non/light drinkers at baseline and follow-up, reference group), persistently moderate (moderate drinkers at baseline and follow-up), persistently high (heavy drinkers at baseline and follow-up), decreasing (moving from heavy drinkers at baseline to moderate or non/light drinkers at follow-up or from moderate drinkers at baseline to non/light drinkers at follow-up), and increasing (moving from non/light drinkers at baseline to moderate or heavy drinkers at follow-up or from moderate drinkers at baseline to heavy drinkers at follow-up).

6.2.3.2. Alcohol consumption at baseline predicting changes in physical activity and daily steps between baseline and follow-up

We used multivariable linear regression models to examine whether alcohol consumption at baseline predicted changes in total physical activity (mins/week) (calculated as Total physical activity follow-up – Total physical activity baseline) and changes in daily steps (calculated as Daily steps follow-up – Daily steps baseline) during follow-up. We estimated the RR (±95% CI) of changing category of physical activity and daily steps over follow-up by alcohol consumption at baseline using log multinomial regression. Physical activity and daily steps at baseline and follow-up were categorised into bottom third, middle third and top third. Categorical change variables were created as follows: persistently low (bottom third at baseline and follow-up, reference group), persistently moderate (middle third at baseline and follow-up), persistently high (top third at baseline and follow-up), decreasing (moving from

top third at baseline to middle or bottom third at follow-up or from middle third at baseline to bottom third at follow-up), and increasing (moving from bottom third at baseline to middle or top third at follow-up or from middle third at baseline to top third at follow-up). Changes in types of physical activity, including leisure time physical activity, transport activity, work-related, walking and household physical activity from baseline to follow-up were generated by the same method.

Sensitivity analyses were conducted excluding participants with an AUD at baseline to prevent potential reverse causation.

6.2.3.3.Covariates

Covariates were included in accordance with purposeful model building procedures, including the putative covariate being associated with the exposure and outcome (e.g. physical activity, daily steps and alcohol consumption) and that the inclusion of the covariate in a model caused a change in the effect estimate of at least 10%. The following potential covariates from baseline and follow-up were considered: age, sex, SES quartile based on area of residence (high, medium-high, medium-low or low), marital status transition (single/separated at both time points, became married/de facto, married/de facto at both time points or became separated/divorced/widowed), parental status transition (no children, first child born since baseline, additional children since baseline or same number of children as baseline), personality traits (Neuroticism-Extraversion-Openness (NEO) five-factor inventory: extraversion, neuroticism, conscientiousness, openness and agreeableness) and social support (Henderson Social Support Score) [283].

6.2.3.4.Missing data

We handled missing data from baseline to follow-up using a combination of IPW and MI [231]. MI using chained equations with 30 estimations was used to replace missing data on covariates. This method was applied to replace missing data on the covariates listed above using the following variables from a previous follow-up of the cohort between 2001 and 2004 on sex, age, smoking status, education, BMI, state of residence, marital status and one variable from 1985 on scholastic ability.

We examined the effect of failure to follow-up on our results using IPW, with weights based on the inverse of the probability of providing follow-up data given variables from a previous adult follow-up in 2001–2004 (sex, age, education, smoking and BMI) or, in a separate analysis, variables from childhood in 1985 (age, sex, BMI, state of residence and three measures of CRF). Unweighted and weighted models, which did not have missing covariates inputted, were then compared. The results of these analyses are presented in the online Appendix material.

There was no evidence of effect modification by sex for any of the analyses; therefore, results for men and women are presented together. Analyses were conducted with the Stata 15.0 (USA) software program.

6.3. Results

The characteristics of the two groups of study participants to examine the bidirectional between the physical activity and alcohol consumption in adulthood are shown in Table 6-1. In general, study participants had comparable characteristics (Table 6-1).

Table 6-1. Characteristics of the study population

Characteristics	**Physical activity predicting changes in alcohol consumption (n=2,031)**		**Alcohol consumption predicting changes in physical activity (n=1,322)**	
	n	% or Mean (S.D.)	n	% or Mean (S.D.)
Female	1,216	60	866	65
Age, years (Mean, ±SD)	1,656	31.4 (2.6)	1,092	31.4 (2.6)
Education				
Tertiary	935	46	672	51
Vocational	576	28	331	25
School only	518	26	318	24
Marital status				
Single	535	26	333	25
Married/living as married	1,441	71	952	72
Divorced/separated/widowed	54	3	37	3
SES quartiles				
Quartile 1	416	27	277	27
Quartile 2	460	29	292	28
Quartile 3	570	37	391	38
Quartile 4	114	7	70	7

S.D., Standard deviation; SES, Socio-economic status; PA, physical activity.

Over 5 years of follow-up from early adulthood (ages 26-36 years) to middle adulthood (ages 31-41 years), average alcohol consumption in grams per day (g/day) decreased. Total physical activity in minutes per week (mins/week) slightly increased, whereas average daily steps (per 10,000 steps per day) decreased over the 5-year follow-up period (Table 6-2). Two-thirds of the sample demonstrated persistently low alcohol consumption while one-fifth of participants moved down in categories of alcohol consumption over 5 years. Meanwhile,

participants were relatively evenly distributed across the 5 categories of changes in physical and changes in daily steps over 5 years of follow-up (Table 6-2).

Table 6-2. Alcohol consumption, physical activity and daily steps from early adulthood (Ages 26-36 Years) into middle-age adulthood (Ages 31-41 Years)

Characteristics	**Physical activity predicting changes in alcohol consumption (n=2,031)**		**Alcohol consumption predicting changes in physical activity (n=1,322)**	
	n	% or Mean (S.D.)	n	% or Mean (S.D.)
Alcohol consumption status				
Baseline alcohol consumption (g/day)	2,031	9.2 (13.1)	1,322	8.5 (11.9)
Follow-up alcohol consumption (g/day)	2,031	7.6 (11.8)	-	-
Change in alcohol consumption (g/day)	2,031	-1.5 (12.1)	-	-
Categorical change in alcohol consumption				
Persistently high	83	4	-	-
Increasing	205	10	-	-
Persistently moderate	139	7	-	-
Decreasing	346	17	-	-
Persistently low	1,258	62	-	-
Physical activity				
Baseline total PA (mins/week)	2,031	753 (505)	1,322	715 (487)
Follow-up total PA (mins/week)	-	-	1,322	732 (487)
Change in total PA (mins/week)	-	-	1,322	17 (544)
Categorical change in PA				
Persistently high	-	-	194	15
Increasing	-	-	350	26
Persistently moderate	-	-	174	13

Characteristics	**Physical activity predicting changes in alcohol consumption (n=2,031)**		**Alcohol consumption predicting changes in physical activity (n=1,322)**	
Decreasing	-	-	326	25
Persistently low	-	-	278	21
Daily steps				
Baseline daily steps (10,000 steps)	1,742	0.90 (0.32)	1,020	0.90 (0.32)
Follow-up daily steps (10,000 steps)	-	-	1,020	0.87 (0.32)
Change in daily steps (10,000 steps)	-	-	1,020	-0.02 (0.34)
Categorical change in daily steps				
Persistently high	-	-	191	19
Increasing	-	-	260	25
Persistently moderate	-	-	138	14
Decreasing	-	-	239	23
Persistently low	-	-	192	19

S.D., Standard deviation; SES, Socio-economic status; PA, physical activity.

6.3.1. Physical activity and daily steps as predictors of changes in alcohol consumption

Among the 2,031 participants who provided data for these analyses, those with higher levels of total physical activity per week measured using the IPAQ at the baseline tended to have an increase in total alcohol consumption over the follow-up (Table 6-3). Those in the middle or top third of total physical activity at the baseline, compared to those in the bottom third of total physical activity at the baseline, were more likely to increase their alcohol consumption (middle third: RR 1.53; 95% CI 1.10, 2.14); top third: RR (95% CI) = 1.47 (1.05, 2.07)) after adjustment for sex, SES, changes in parental status and changes in marital status (Table 6-3).

Table 6-3. Log multinomial regression analyses of the association between baseline physical activity, types of physical activity in total minutes per week, daily steps (x 10,000 steps) and categorical changes in alcohol consumption over 5 years of follow-up

	Categorical changes of alcohol consumption							
	Persistently moderate		**Persistently high**		**Decreasing**		**Increasing**	
Exposures	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Total PA								
Bottom third	Ref.		Ref.		Ref.			
Middle third	1.12 (0.76, 1.64)	0.570	0.96 (0.57, 1.61)	0.866	0.99 (0.78, 1.26)	0.960	1.53 (1.10, 2.14)	<0.05
Top third	0.93 (0.62, 1.40)	0.740	1.11 (0.67, 1.84)	0.691	1.09 (0.86, 1.37)	0.474	1.47 (1.05, 2.07)	<0.05
P-trend		*0.760*		0.694		0.479		<0.05
Leisure time PA								
Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	0.96 (0.59, 1.59)	0.886	0.65 (0.36, 1.18)	0.158	1.51 (1.11, 2.06)	<0.01	1.18 (0.81, 1.75)	0.380
Top third	1.34 (0.83, 2.15)	0.226	0.37 (0.18, 0.77)	<0.01	1.57 (1.15, 2.15)	<0.01	0.97 (0.64, 1.48)	0.902
P-trend		*0.200*		*<0.01*		*<0.01*		*0.085*
Transport PA								
Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	1.07 (0.65, 1.76)	0.796	1.48 (0.76, 2.89)	0.248	1.07 (0.82, 1.41)	0.604	0.82 (0.55, 1.22)	0.339
Top third	1.53 (0.99, 2.38)	0.057	1.52 (0.80, 2.90)	0.203	0.98 (0.75, 1.28)	0.879	0.92 (0.64, 1.34)	0.678
P-trend		*<0.05*		*0.210*		*0.864*		*0.678*
Walking PA								

Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	1.28 (0.80, 2.06)	0.302	1.48 (0.74, 2.95)	0.263	1.09 (0.83, 1.43)	0.554	0.79 (0.53, 1.18)	0.249
Top third	1.52 (0.98, 2.33)	0.059	1.78 (0.95, 3.35)	0.071	1.08 (0.84, 1.40)	0.549	0.91 (0.63, 1.30)	0.593
P-trend		*0.058*		*0.071*		*0.549*		*0.580*
Household PA								
Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	1.04 (0.69, 1.59)	0.839	0.92 (0.49, 1.73)	0.791	1.09 (0.85, 1.40)	0.484	1.08 (0.74, 1.58)	0.673
Top third	1.13 (0.71, 1.78)	0.608	1.33 (0.71, 2.48)	0.374	0.87 (0.65, 1.16)	0.333	1.17 (0.79, 1.73)	0.424
P-trend		*0.593*		*0.419*		*0.451*		*0.422*
Daily steps (10,000 steps)								
Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	1.11 (0.73, 1.69)	0.619	1.21 (0.68, 2.17)	0.521	1.21 (0.93, 1.57)	0.158	1.07 (0.74, 1.53)	0.726
Top third	1.05 (0.68, 1.61)	0.837	1.31 (0.73, 2.33)	0.362	1.36 (1.05, 1.76)	<0.05	1.45 (1.03, 2.03)	<0.05
P-trend		*0.835*		*0.364*		*<0.05*		*<0.05*

RR, Relative risk; CI, Confidence interval; PA, Physical activity

"Persistently low" is the excluded alcohol consumption change category

[†] Adjusted for sex, SES status, cardiorespiratory fitness, parental status transition, marital status transition

Those in the middle third of leisure time physical activity at the baseline, compared to those in the bottom third of leisure time physical activity at the baseline, were more likely to decrease their alcohol consumption during the follow-up period. Other types of physical activity at the baseline were not associated with changes in alcohol consumption over the follow-up (Table 6-3).

Similar results were seen with daily steps at the baseline measured by pedometers used as the measure of physical activity (Table 6-3). Those in the top third of daily steps at the baseline, compared to those in the bottom third of daily steps at the baseline, were significantly more likely to increase and decrease their alcohol consumption. After adjusting for sex and changes in marital status, the results for the increasing alcohol consumption groups were attenuated (Table 6-3).

Applying IPW to account for failure to follow-up did not change the results (Appendix Table 6-10).

6.3.2. *Alcohol consumption as a predictor of changes in physical activity and daily steps*

Among the 1,322 participants who provided data for these analyses, those with higher levels of alcohol consumption at the baseline tended to have a decrease in total physical activity and daily steps over the follow-up. There was a significantly inverse linear association between total alcohol consumption by g/day at the baseline and changes in total minutes of physical activity per week over the 5 years of follow-up (Table 6-4). There was a significant association between higher levels of alcohol consumption at the baseline and decreased work-related physical activity in mins/week, whereas no significant associations were observed in the changes of other domain-specific physical activities over the follow-up period based on baseline alcohol consumption (Table 6-4).

There were also a significant negative association between baseline alcohol consumption in g/day and daily steps over the 5 years of follow-up (Table 6-4).

Table 6-4. Multivariable linear regression analyses of the association between baseline alcohol consumption and changes in minutes per week of total physical activity, types of physical activity and daily steps (x 10,000 steps) over 5 years of follow-up

	Unadjusted		**Adjusted**	
	β (95% CI) †	P-value	β (95% CI) †	P-value
Baseline alcohol consumption	**Total PA (mins/week)**			
0 g/day	Ref.		Ref.	
>0-10 g/day	-122.1 (-203.4, -40.8)	<0.01	-129.2 (-211.2, -47.3)	<0.01
>10-20 g/day	-153.2 (-249.4, -57.0)	<0.01	-165.6 (-263.2, -68.0)	<0.01
>20 g/day	-130.2 (-251.4, -9.0)	<0.05	-137.6 (-260.4, -14.8)	<0.05
P-trend		*<0.05*		*<0.01*
Baseline alcohol consumption	**Leisure time PA (mins/week)**			
0 g/day	Ref.		Ref.	
>0-10 g/day	-29.7 (-62.7, 3.32)	0.078	-26.6 (-60.0, 6.9)	0.119
>10-20 g/day	-41.6 (-80.6, -2.5)	<0.05	-32.8 (-72.6, 7.0)	0.106
>20 g/day	-10.7 (-59.9, 38.5)	0.670	-3.8 (-53.9, 46.3)	0.883
P-trend		*0.318*		*0.590*
Baseline alcohol consumption	**Transport PA (mins/week)**			
0 g/day	Ref.		Ref.	
>0-10 g/day	-24.6 (-53.8, 4.44)	0.097	-28.9 (-58.5, 0.7)	0.056
>10-20 g/day	-17.5 (-51.9, 17.0)	0.320	-23.6 (-58.9, 11.6)	0.189
>20 g/day	-18.0 (-61.3, 25.4)	0.417	-21.6 (-66.0, 22.7)	0.339
P-trend		*0.517*		*0.392*
Baseline alcohol consumption	**Walking PA (mins/week)**			
0 g/day	Ref.		Ref.	
>0-10 g/day	-22.8 (-51.1, 5.5)	0.115	-27.3 (-56.1, 1.5)	0.063
>10-20 g/day	-23.0 (-56.5, 10.5)	0.178	-28.9 (-63.2, 5.4)	0.099
>20 g/day	-15.1 (-57.3, 27.1)	0.482	-18.3 (-61.5, 24.8)	0.404
P-trend		*0.413*		*0.320*

Baseline alcohol consumption	**Household PA (mins/week)**			
0 g/day	Ref.		Ref.	
>0-10 g/day	12.1 (-34.8, 59.0)	0.612	-3.3 (-50.1, 43.5)	0.890
>10-20 g/day	10.8 (-44.7, 66.3)	0.702	-12.2 (-68.0, 43.5)	0.667
>20 g/day	33.0 (-36.9, 102.9)	0.355	3.6 (-66.5, 73.7)	0.920
P-trend		*0.432*		*0.888*
Baseline alcohol consumption	**Work-related PA (mins/week)**			
0 g/day	Ref.		Ref.	
>0-10 g/day	-79.9 (-134.6, -25.1)	<0.01	-70.5 (-125.8, -15.1)	<0.05
>10-20 g/day	-105.0 (-170.0, -40.3)	<0.001	-96.9 (-162.9, -31.0)	<0.01
>20 g/day	-134.5 (-216.1, -52.9)	<0.001	-115.8 (-198.7, -32.9)	<0.01
P-trend		*<0.001*		*<0.01*
Baseline alcohol consumption	**Daily steps (x 10,000 steps) ***			
0 g/day	Ref.		Ref.	
>0-10 g/day	-0.08 (-0.14, -0.02)	<0.01	-0.08 (-0.14, -0.02)	<0.01
>10-20 g/day	-0.09 (-0.16, -0.02)	<0.01	-0.09 (-0.16, -0.02)	<0.05
>20 g/day	-0.12 (-0.20, -0.03)	<0.01	-0.11 (-0.20, -0.02)	<0.05
P-trend		*<0.01*		*<0.05*

Abbreviation: CI=confidence interval; PA=physical activity

† β=beta coefficients expressed in unit change of minutes per week of total physical activity 5 years later compared to baseline; ***** β=beta coefficients expressed in unit change of daily steps (x 10,000 steps) 5 years later compared to baseline

Compared to non-drinkers at the baseline, those with higher levels of alcohol consumption at the baseline were less likely to increase their physical activity during the follow-up. Results persisted after adjusting for potential explanatory factors of changes in parental and marital status (Table 6-5). Similarly, those with higher levels of alcohol consumption at the baseline were more likely to decrease their daily steps during the follow-up. Similar results persisted after adjusting for parental status transition, which was the only covariates that meet the criteria for inclusion in the final model (Table 6-5).

Results using categorical variables showed that those consuming light to moderate levels of alcohol at the baseline were more likely to have persistently high levels of leisure time physical activity, transport-related activity and household-related activity during the follow-up, compared to non-drinkers (Table 6-6). In contrast, compared to those that were non-drinkers at baseline, those that were light-moderate drinkers at the baseline were more likely to decrease their work-related physical activity and household-related physical activity on average over the 5 years of follow-up (Table 6-6). For PA measured with pedometers, heavy drinkers at baseline were more likely to remain in the persistently high daily steps category compared to non-drinkers (Table 6-6).

Applying inverse probability weights made small differences to these results on physical activity changes, but the results on daily steps did not remain statistically significant (Appendix Table 6-11).

Table 6-5. Log multinomial regression analyses of the association between baseline total alcohol consumption by grams per day and categorical changes in minutes of physical activity per week and categorical changes in daily steps over 5 years of follow-up

	Categorical changes of PA							
	Persistently moderate		**Persistently high**		**Decreasing**		**Increasing**	
Outcome: Total PA	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Exposures								
Alcohol consumption								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	1.22 (0.80, 1.87)	0.348	1.24 (0.84, 1.83)	0.273	1.28 (0.96, 1.71)	0.097	0.80 (0.64, 1.00)	0.054
>10-20 g/day	1.54 (0.97, 2.45)	0.069	0.99 (0.62, 1.59)	0.965	1.32 (0.95, 1.84)	0.094	0.77 (0.58, 1.02)	0.068
>20 g/day	1.04 (0.55, 1.97)	0.900	1.58 (0.95, 2.62)	0.076	1.20 (0.79, 1.81)	0.397	0.66 (0.44, 0.98)	<0.05
P-trend		*0.375*		*0.358*		*0.317*		*<0.05*
Outcome: Daily steps								
Exposures	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Alcohol consumption								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	1.00 (0.64, 1.56)	0.999	1.25 (0.84, 1.87)	0.269	1.60 (1.10, 2.32)	<0.05	0.83 (0.64, 1.09)	0.184

>10-20 g/day	1.08 (0.64, 1.82)	0.767	1.29 (0.81, 2.05)	0.277	1.57 (1.03, 2.40)	<0.05	0.77 (0.55, 1.08)	0.126
>20 g/day	1.35 (0.74, 2.46)	0.332	1.90 (1.16, 3.12)	<0.01	1.39 (0.82, 2.36)	0.219	0.65 (0.40, 1.05)	0.076
P-trend		*0.350*		*<0.05*		*0.232*		*0.057*

RR, Relative risk; CI, Confidence interval; PA, Physical activity

"Persistently low" is the excluded physical activity change category

[†] Adjusted for cardiorespiratory fitness, parental status transition, marital status transition

Table 6-6. Log multinomial regression analyses of the association between baseline alcohol consumption by grams per day and categorical changes in domains of physical activity in minutes per week over 5 years of follow-up

	Categorical changes of PA							
	Persistently moderate		Persistently high		Decreasing		Increasing	
	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Leisure time PA								
Alcohol consumption								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	1.58 (1.04, 2.39)	<0.05	1.69 (1.08, 2.64)	<0.05	1.19 (0.90, 1.58)	0.215	0.86 (0.68, 1.10)	0.237
>10-20 g/day	1.23 (0.75, 2.02)	0.413	1.80 (1.10, 2.92)	<0.05	1.31 (0.95, 1.80)	0.098	0.90 (0.67, 1.22)	0.497
>20 g/day	1.30 (0.72, 2.36)	0.391	1.48 (0.81, 2.70)	0.198	1.17 (0.79, 1.75)	0.433	1.06 (0.75, 1.50)	0.734
P-trend		*0.840*		*0.314*		*0.356*		*0.727*
Transport PA								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	0.85 (0.58, 1.25)	0.411	1.64 (1.08, 2.49)	<0.05	1.19 (0.92, 1.53)	0.187	0.88 (0.68, 1.14)	0.339
>10-20 g/day	0.96 (0.60, 1.53)	0.858	1.37 (0.85, 2.21)	0.199	1.28 (0.95, 1.72)	0.106	1.02 (0.74, 1.39)	0.916
>20 g/day	0.83 (0.45, 1.52)	0.538	1.44 (0.83, 2.52)	0.197	1.20 (0.83, 1.72)	0.333	1.03 (0.71, 1.51)	0.863

	Categorical changes of PA							
	Persistently moderate		Persistently high		Decreasing		Increasing	
P-trend		*0.781*		*0.648*		*0.231*		*0.588*
Walking PA								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	0.92 (0.61, 1.40)	0.698	1.59 (1.05, 2.41)	<0.05	1.22 (0.94, 1.57)	0.129	0.89 (0.69, 1.14)	0.353
>10-20 g/day	1.10 (0.67, 1.79)	0.707	1.36 (0.85, 2.20)	0.203	1.28 (0.95, 1.73)	0.101	0.97 (0.71, 1.32)	0.838
>20 g/day	1.11 (0.61, 2.02)	0.733	1.44 (0.82, 2.50)	0.201	1.27 (0.89, 1.82)	0.193	0.85 (0.57, 1.27)	0.425
P-trend		*0.533*		*0.582*		*0.164*		*0.691*
Household PA								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	0.99 (0.66, 1.49)	0.958	1.03 (0.80, 1.31)	0.844	1.26 (0.97, 1.65)	0.088	0.77 (0.60, 0.99)	<0.05
>10-20 g/day	1.27 (0.80, 2.01)	0.307	0.65 (0.45, 0.94)	<0.05	1.38 (1.01, 1.89)	<0.05	0.88 (0.65, 1.18)	0.393
>20 g/day	0.83 (0.44, 1.59)	0.582	0.60 (0.35, 1.05)	0.074	1.44 (1.00, 2.06)	0.051	0.76 (0.51, 1.15)	0.193
P-trend		*0.805*		*<0.05*		*<0.05*		*0.424*
Work-related PA								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	1.66 (0.74, 3.69)	0.219	1.77 (1.14, 2.76)	<0.05	1.44 (1.01, 2.05)	<0.05	0.85 (0.65, 1.09)	0.204

	Categorical changes of PA							
	Persistently moderate		Persistently high		Decreasing		Increasing	
>10-20 g/day	0.95 (0.35, 2.63)	0.924	2.22 (1.38, 3.57)	<0.01	1.36 (0.91, 2.02)	0.132	0.85 (0.62, 1.17)	0.314
>20 g/day	1.93 (0.69, 5.44)	0.582	2.31 (1.35, 3.96)	<0.01	1.47 (0.93, 2.33)	0.099	0.73 (0.47, 1.13)	0.161
P-trend		*0.689*		*<0.01*		*0.275*		*0.224*

RR, Relative risk; CI, Confidence interval; PA, Physical activity

"Persistently low" is the excluded alcohol consumption change category

[†] Adjusted for sex, SES status, cardiorespiratory fitness, parental status transition, marital status transition

6.4. Discussion

We examined the longitudinal associations between physical activity and alcohol consumption in a cohort of men and women over a 5-year period from young to middle-age adulthood. We found that greater minutes of total physical activity per week at the baseline were associated with consuming significantly more alcohol 5 years later. In contrast, people that drank more alcohol at the baseline were less likely to increase their physical activity over the 5 years of follow-up. Results were largely similar when we used the objective measure of steps per day measured by a pedometer instead of self-reported physical activity by questionnaires. The physical activity-alcohol relationship appeared to differ depending on the types of physical activity. While higher leisure time physical activity at the baseline was associated with a decrease in alcohol consumption, other types of physical activity at the baseline were not associated with changes in alcohol consumption over the follow-up period. Those that consumed light to moderate levels of alcohol at the baseline were more likely to have persistently high levels of leisure-time, transport and household physical activity during the follow-up compared to non-drinkers, whereas those with higher levels of alcohol consumption at the baseline were more likely to decrease their work-related and household-related physical activities during the follow-up period.

We found that greater total daily levels of physical activity measured using either questionnaires or pedometers at the baseline were associated with an increase in alcohol consumption over the follow-up period. Our findings were consistent with several studies that showed a positive linear association between total physical activity and alcohol, in which higher physical activity was cross-sectionally and longitudinally associated with higher alcohol consumption in the general population [82, 83], This is also consistent with the findings in the previous chapter demonstrating that higher physical activity and greater fitness in childhood was associated with greater alcohol consumption in adulthood. The relationship between physical activity and alcohol use overtime has been suggested to jointly contribute to health outcomes [71, 72, 284]. These studies used measures of total physical activity, which is made up of several domains, using questionnaires. We found that the PA-alcohol relationship differed depending on the type of PA. While higher leisure-time physical activity at baseline was associated with a decrease in alcohol consumption, other types of physical activity at baseline were not associated with changes in alcohol consumption over follow-up. Our results suggest that studies of the association between alcohol consumption and health outcomes may

need to consider the dynamic nature of the association with physical activity over the life course to properly estimate any direct effects of these exposures.

We also examined the possibility that the levels of alcohol consumption at baseline would be associated with changes in physical activity overtime. We found that baseline levels of alcohol consumption had an inverse linear association with total physical activity and daily steps over 5 years of follow-up. People that consumed light to moderate amounts of PA at baseline more often had persistently moderate or high levels of leisure-time PA at follow-up compared to those that did not drink alcohol. Of note is that we did not find that possible explanatory variables such as personality or social support could account for these associations. These findings are potentially important for studies seeking to estimate the direct effects of alcohol consumption on health outcomes. It is possible that previous studies attempting to estimate the causal effect of alcohol consumption on health outcomes, particularly cardiovascular and metabolic outcomes, may have been unable to properly account for the dynamic nature of the associations between these two variables. This may have contributed to the over-estimation of the health benefits of light to moderate alcohol consumption, as highlighted by others recently [80].

An important factor to consider when interpreting results from bidirectional analyses is the difference in random measurement error associated with the exposure and outcome measures. Misclassification of alcohol consumption may have occurred using the FFQ. However, self-reported alcohol intake by FFQ has been shown to be reliable and valid in young adults [16]. IPAQ has previously been shown to be valid for assessing physical activity in adults; the correlation between IPAQ and objectively measured physical activity by accelerometry is $p=0.37$ for men and $p=0.43$ for women ($P<0.01$), indicating a moderate correlation [285]. In contrast, daily steps were measured very precisely [286]. The bias introduced by marked differences in measurement error depends on whether the variable measured with the least precision is analysed as the exposure or outcome variable. When the imprecise measure is analysed as the exposure variable, it acts to bias the effect estimate towards the null. In contrast, when the imprecise measure is analysed as the outcome variable, the magnitude of the effect is estimated accurately, but the standard error of the estimate is increased, and the corresponding CIs widened, making the result less likely to be significant [287]. Consequently, under the assumption that the associations between physical activity and alcohol consumption are bidirectionally equivalent, because physical activity is measured with greater precision it will appear that it is the stronger predictor of alcohol consumption rather than vice versa. Although a direct comparison of regression estimates is difficult, our

findings suggest that alcohol consumption and participation in physical activity are closely linked. Future studies with better objective measures of physical activity, such as accelerometers, are needed to confirm our findings.

There are several plausible explanations for our findings. There may be some biological basis to the relationship between physical activity and alcohol consumption with these activities having some similar effects on the brain [76]. For example, exercise and alcohol intake represent rewarding stimuli that invoke activity in the brain's mesocorticolimbic pathway [288-291]. Physical activity has been shown to increase the release of dopamine and other monoamines, such as serotonin and norepinephrine [288, 289] or endogenous opioids, such as endorphins [290, 291]. Meanwhile, alcohol consumption has been shown to enhance dopamine activity in the mesocorticolimbic pathway [292] and endogenous opioid activity [293]. These overlapping effects have led some to suggest that physical activity should be a component of treatment programs for alcohol abuse [76]. It is therefore possible that people motivated by these feelings of reward undertake these two activities to achieve these feelings. In a review researchers' proposed possible joint motivations of drinking and physical activity defined as 'work hard, play hard', 'celebration', 'body image', and 'guilt' [76]. While 'work hard, play hard' and 'celebration' motives would place physical activity as the precursor of alcohol consumption [294, 295], 'body image' and 'guilt' motives would place more alcohol consumption as the precursor of more physical activity [296, 297]. With this context, drinking and physical activity may not be causally associated, but instead reflect a general motivational tendency that accounts for both activities. The acute and long-term biological effects of alcohol including the dehydration, disruption of sleep patterns, and effects on growth hormones or heart rate may reduce engagement in physical activity [298]. These mechanisms are likely to mostly be related to leisure-time activities, which is consistent with our finding that people doing moderate leisure-time PA at baseline were more likely to decrease their alcohol consumption over time and that light to moderate activity was more common in people that drank only moderate amounts. One possibility for the association is that these behaviours were undergoing change at a time when a host of other 'life stage transitions' are occurring. However, the relationships between alcohol consumption and physical activity persisted after adjustment for life-stage transition factors in adulthood. This indicates that the effect of is not solely due to concurrent life-stage transitions. Future studies attempting to understand the biological and social mechanisms linking these behaviours should be considered.

Our study has several important strengths, including the large sample size, objective measures of physical activity, consideration of different domains of PA and long-term follow-up. Assessment of physical activity by self-report generally leads to an overestimate of physical activity levels, but these self-report questionnaires have been shown to be sensitive to changes in physical activity [299]. Our study also has several limitations. Underreporting of alcohol consumption may have occurred with self-reported alcohol intake by FFQ. Although we were able to adjust for important confounders, we cannot exclude the possibility of residual confounding by unmeasured or imprecisely measured factors.

6.5. Conclusions

There appears to be bidirectional associations between alcohol consumption and physical activity in adulthood. Given the individual, and potentially joint, contributions of these factors to a range of health outcomes careful modelling of their dynamic relationship over the life course must be considered when attempting to estimate the causal association between either physical activity or alcohol with health outcomes.

6.6. Appendix 6. Additional Tables and Figures

Table 6-7. Multivariable linear regression analyses of the association between baseline physical activity and changes in alcohol consumption over 5 years of follow-up

	Unadjusted		Adjusted	
	β (95% CI) †	P-value	β (95% CI) †	P-value
Baseline PA, daily steps				
Total weekly PA				
Bottom third	Ref.		Ref.	
Middle third	0.37 (-0.91, 1.64)	0.573	0.46 (-0.81, 1.75)	0.474
Top third	-0.07 (-1.36, 1.22)	0.913	-0.18 (-1.48, 1.11)	0.780
P-trend		*0.924*		*0.797*
Daily steps (10,000 steps)				
Bottom third	Ref.		Ref.	
Middle third	0.47 (-0.88, 1.82)	0.498	0.38 (-0.97, 1.73)	0.582
Top third	-0.85 (-2.21, 0.51)	0.222	-0.88 (-2.25, 0.49)	0.206
P-trend		*0.229*		*0.215*

† β=beta coefficients expressed in unit change of grams of alcohol consumption per day on average 5 years later compared to baseline

Abbreviation: CI=confidence interval; PA=physical activity

[†] Adjusted for sex, parental status transition, marital status transition

Table 6-8. Log multinomial regression analyses applying multiple imputation of the association between baseline physical activity, types of physical activity in total minutes per week, daily steps (x 10,000 steps) and categorical changes in alcohol consumption over 5 years of follow-up

	Categorical changes of alcohol consumption							
	Persistently moderate		**Persistently high**		**Decreasing**		**Increasing**	
Exposures	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Total PA								
Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	1.01 (0.63, 1.48)	0.887	1.18 (0.62, 2.27)	0.613	1.03 (0.78, 1.35)	0.855	1.48 (1.02, 2.20)	<0.05
Top third	0.88 (0.52, 1.28)	0.371	1.24 (0.65, 2.38)	0.518	1.13 (0.87, 1.47)	0.364	1.36 (1.01, 2.05)	<0.05
P-trend		*0.939*		*0.495*		*0.112*		*<0.05*
Daily steps (10,000 steps)								
Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	1.16 (0.70, 1.94)	0.571	1.27 (0.62, 2.61)	0.521	1.42 (0.97, 2.08)	0.905	1.03 (0.64, 1.66)	0.905
Top third	0.94 (0.55, 1.60)	0.809	1.33 (0.65, 2.73)	0.431	1.66 (1.14, 2.40)	<0.05	1.62 (1.04, 2.53)	<0.05
P-trend		*0.819*		*0.431*		*<0.01*		*<0.05*

RR, Relative risk; CI, Confidence interval; PA, Physical activity

"Persistently low" is the excluded alcohol consumption change category

† Adjusted for sex, SES status, cardiorespiratory fitness, parental status transition, marital status transition

Table 6-9. Log multinomial regression analyses applying multiple imputation of the association between baseline total alcohol consumption by grams per day and categorical changes in minutes of physical activity per week and categorical changes in daily steps over 5 years of follow-up

	Categorical changes of PA							
	Persistently moderate		**Persistently high**		**Decreasing**		**Increasing**	
Outcome: Total PA								
Exposures	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Alcohol consumption								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	1.61 (0.93, 2.80)	0.091	1.81 (1.07, 3.07)	<0.05	1.70 (1.08, 2.70)	<0.05	1.02 (0.71, 1.63)	0.173
>10-20 g/day	2.12 (1.12, 4.00)	<0.05	1.58 (0.83, 3.01)	0.164	1.84 (1.08, 3.17)	<0.05	1.00 (0.64, 1.60)	0.078
>20 g/day	1.17 (0.51, 2.67)	0.704	2.07 (1.00, 4.30)	0.051	1.37 (1.01, 2.67)	<0.05	0.73 (0.38, 0.99)	<0.05
P-trend		*0.260*		*0.108*		*<0.05*		*0.231*
Outcome: Daily steps								
Exposures	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Alcohol consumption								
0 g/day	Ref.		Ref.		Ref.		Ref.	

>0-10 g/day	1.23 (0.61, 2.48)	0.558	1.81 (0.90, 3.64)	0.098	1.67 (1.03, 3.15)	<0.05	1.44 (0.78, 2.67)	0.236
>10-20 g/day	1.13 (0.48, 2.68)	0.777	2.07 (0.91, 4.67)	0.081	1.50 (1.01, 3.20)	<0.05	1.46 (0.70, 3.05)	0.310
>20 g/day	2.06 (0.67, 6.31)	0.206	3.80 (1.33, 10.86)	<0.05	1.93 (0.68, 5.49)	0.219	2.04 (0.74, 5.59)	0.167
P-trend		*0.322*		*<0.05*		*0.102*		*0.187*

RR, Relative risk; CI, Confidence interval; PA, Physical activity

"Persistently low" is the excluded physical activity change category

[†] Adjusted for cardiorespiratory fitness, parental status transition, marital status transition

Table 6-10. Log multinomial regression analyses applying inverse probability weighting of the association between baseline physical activity, types of physical activity in total minutes per week, daily steps (x 10,000 steps) and categorical changes in alcohol consumption over 5 years of follow-up

	Categorical changes of alcohol consumption							
	Persistently moderate		**Persistently high**		**Decreasing**		**Increasing**	
Exposures	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Total PA								
Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	0.88 (0.54, 1.41)	0.587	1.39 (0.69, 2.81)	0.351	1.02 (0.76, 1.39)	0.878	1.51 (1.01, 2.34)	<0.05
Top third	0.73 (0.45, 1.18)	0.192	1.24 (0.62, 2.47)	0.542	1.15 (0.87, 1.53)	0.322	1.40 (1.01, 2.17)	<0.05
P-trend		*0.185*		*0.558*		*0.321*		*<0.05*
Daily steps (10,000 steps)								
Bottom third	Ref.		Ref.		Ref.		Ref.	
Middle third	1.08 (0.65, 1.78)	0.776	1.22 (0.59, 2.51)	0.589	1.38 (0.96, 1.85)	0.081	1.10 (0.69, 1.75)	0.701
Top third	0.81 (0.47, 1.40)	0.454	1.16 (0.56, 2.41)	0.689	1.45 (1.05, 2.00)	<0.05	1.55 (1.01, 2.41)	<0.05
P-trend		*0.428*		*0.705*		*<0.05*		*<0.05*

RR, Relative risk; CI, Confidence interval; PA, Physical activity

"Persistently low" is the excluded alcohol consumption change category

† Adjusted for sex, SES status, cardiorespiratory fitness, parental status transition, marital status transition

* Variables for weights were from current follow-up in 2004-06 and included age, sex, education level, smoking, BMI, state of residence. See methods for details.

Table 6-11. Log multinomial regression analyses applying inverse probability weighting of the association between baseline total alcohol consumption by grams per day and categorical changes in minutes of physical activity per week and categorical changes in daily steps over 5 years of follow-up

	Categorical changes of PA							
	Persistently moderate		Persistently high		Decreasing		Increasing	
Outcome: Total PA								
Exposures	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Alcohol consumption								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	1.15 (0.71, 1.87)	0.571	1.36 (0.89, 2.07)	0.153	1.14 (0.84, 1.55)	0.392	0.83 (0.64, 1.07)	0.156
>10-20 g/day	1.41 (0.83, 2.42)	0.204	1.13 (0.68, 1.87)	0.642	1.26 (0.89, 1.79)	0.195	0.74 (0.54, 0.99)	<0.05
>20 g/day	1.09 (0.54, 2.21)	0.808	1.81 (1.06, 3.10)	<0.05	1.08 (0.68, 1.70)	0.742	0.63 (0.40, 0.98)	<0.05
P-trend		*0.454*		*0.147*		*0.461*		*<0.05*

	Categorical changes of PA							
	Persistently moderate		Persistently high		Decreasing		Increasing	
Outcome: Daily steps								
Exposures	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value	RR (95% CI) †	P-value
Alcohol consumption								
0 g/day	Ref.		Ref.		Ref.		Ref.	
>0-10 g/day	0.94 (0.55, 1.62)	0.832	1.06 (0.64, 1.77)	0.824	1.10 (0.71, 1.68)	0.684	1.07 (0.72, 1.59)	0.724
>10-20 g/day	0.83 (0.43, 1.62)	0.587	1.17 (0.67, 2.05)	0.583	1.09 (0.67, 1.76)	0.730	1.00 (0.63, 1.59)	0.993
>20 g/day	0.94 (0.42, 2.07)	0.873	1.74 (0.93, 3.26)	0.084	0.92 (0.50, 1.70)	0.798	1.06 (0.60, 1.89)	0.841
P-trend		*0.672*		*0.067*		*0.814*		*0.979*

RR, Relative risk; CI, Confidence interval; PA, Physical activity

"Persistently low" is the excluded physical activity change category

* Variables for weights were from current follow-up in 2004-06 and included age, sex, education level, smoking, BMI, state of residence. See methods for details.

Chapter 7

Childhood physical activity and sport participation as predictors of early adulthood alcohol consumption and alcohol use disorders: A 20-year cohort study

7 Chapter 7. Childhood physical activity, sport participation as predictors of early adulthood alcohol consumption and alcohol use disorders: A 20-year cohort study

7.1. Introduction

Levels of alcohol use and physical activity are both associated with mortality and morbidity from a range of diseases [71, 72]. Greater levels of physical activity (PA) undoubtedly reduce the risk of a range of chronic diseases [300]. The associations between alcohol and chronic disease are more complex. There are potentially J-shaped associations with health benefits in those consuming moderate amounts of alcohol but not low or high amounts of alcohol [79, 80]. It is of potential public health and clinical significance that there is evidence indicating a complex relationship between alcohol use and physical activity.

Among a limited number of studies in adults, some have shown a positive linear association between measures of total daily or weekly physical activity (e.g. combination of leisure, work and household and transport physical activities) and alcohol [82, 83], whereas others have found no association [84, 85]. In a cross-sectional study of people aged 18 years and older in the USA, it was reported that higher levels of daily alcohol consumption and occasional binge drinking measured by questionnaires were associated with higher minutes of total physical activity per week [82]. Similarly, a cross-sectional study of men and women aged 17–38 years old in Greece showed that higher alcohol consumption per week assessed by a daily drinking questionnaire were associated with higher levels of weekly physical activity [83]. In contrast, cross-sectional and longitudinal analyses among the Finnish adult population revealed that weekly alcohol consumption was not associated with frequency of total physical activity [84]. A limitation of these previous findings is that most examined self-reported physical activity, which might be prone to measurement error, and there were limited longitudinal studies. There are limited insights into specific types of physical activity or objective measures of physical activity and their relationship with alcohol consumption in adulthood.

In contrast to the positive association between self-reported physical activity and alcohol consumption in adults, several longitudinal studies have indicated that physical activity in

early life might protect against the development of AUDs in adulthood. As described in the introduction, persistent physical inactivity in adolescence was associated with a 2-fold increased risk of alcohol use problems later in life compared to being persistently active in a study of 4,240 people in Finland followed from the age of 16–18 years old to the age of 22–27 years old [86]. Similarly, a recent finding from a cohort study of 18,359 people in Denmark followed for 20 years showed that higher leisure time physical activity during early life (20 years and above) appeared to be protective against AUDs later in life [87]. Authors have proposed that individual characteristics (e.g. personality or and social mechanisms) account for the association [88]. There have been few studies that have controlled for a wide range of potential explanatory factors; so, the mechanisms are unclear [85, 88]. Studies have also tended to examine total or leisure time physical activity [86, 87] but not other types of activity. Examining the types of physical activity and alcohol consumption could further our understanding of this relationship.

Sports are a specific type of physical activity that have been reported to have variable associations with alcohol consumption. As summarised in the introduction, cross-sectional studies showed that participation in sports was associated with lower [89, 90] or higher levels of alcohol use [91, 92], but others found no association at all [93] among adolescents. In one cross-sectional study of 460 people aged 16–24 years old in France it was found that, compared to individual sport, participation in team sports was positively correlated with alcohol use [90]. Greater childhood sport participation measured using questionnaires in approximately 1,000 children aged 12 years old was associated with greater adulthood alcohol consumption measured at 18 years of age and at 28 years of age; however, the authors suggested that this was not necessarily a direct effect [94]. It is likely that the association between sport activity and alcohol consumption is explained by other factors such as, personal beliefs but most studies did not measure these variables [94]. There is therefore a need for longitudinal studies from childhood to adulthood that include potential explanatory factors to understand this relationship. Such findings could contribute to interventions to address drinking in sports clubs.

Of consideration when examining the association between physical activity and alcohol consumption is the potential role of CRF. CRF is a measure of the capacity of the cardiovascular system to transport oxygen and the capacity of the muscle to use it [159]. A person's CRF reflects genetic, environmental or behavioural factors [75]. CRF is modifiable through increased or decreased participation in physical activity [159]. For example, CRF is known to be associated with self-reported physical activity and sport participation among

children [161]. Of relevance to studies of alcohol consumption and physical activity is that some cross-sectional studies among the general population have reported that alcohol consumption has a U-shaped association with CRF [75, 162]. In contrast, other cross-sectional and longitudinal studies of adults reported no association [163, 164]. As shown in Chapter 3, we recently found that CRF was an influential covariate in the relationship between alcohol consumption and some cardiovascular risk factors, including high BP, lipid abnormalities and central obesity [160]. As with associations between physical activity and alcohol consumption, there is uncertainty regarding the mechanisms linking alcohol and CRF [75]. Examining the relationships between childhood CRF and adulthood alcohol consumption including AUDs with consideration of potential explanatory factors should provide a better understanding of the nature of these associations.

Our aim was to examine the association between childhood physical activity and alcohol consumption and AUDs in early adulthood, with consideration of objective measures of CRF.

7.2. Methods

7.2.1. Study population

At the baseline, 8,498 children and adolescents participated in the 1985 ASHFS, a nationally representative study of youth aged 7–15 years in Australia. A two-stage probability sampling process was used, which involved selecting schools (government, Catholic and independent) with a probability proportional to size (n=109, 90.1% response rate) and then using simple random sampling to select 10 boys and girls from each age strata within the schools (n=8,498, 67.5% response rate).

At the follow-up, 6,840 participants (80%) were traced from current and historical electoral rolls, electronic telephone directories and contact with classmates as part of the CDAH study. Of those individuals found, 5,170 agreed to participate in the follow-up (61% of the baseline sample), and physical activity or CRF data were collected from 2,905 (34% of the baseline sample; mean age, 31.9 (SD=2.1) years).

7.2.2. *Baseline physical activity, sport participation and cardiorespiratory fitness measures*

Questionnaires were completed by participants in 1985 when aged 9–15 years (n=6,412) on self-reported past week duration and frequency of discretionary sport or exercise (leisure activity), walking and cycling to and from school (active transport), school physical education and school sport. For each activity, frequency was multiplied by duration to estimate min/week and activities were summed to estimate total weekly physical activity (mins/week). Participants also reported the number of sports that they had played for an organised team, group, club or school in the past year (i.e., past year sport participation). These were classified as team sports and other sports (see Appendix Table 7-18).

At the baseline, two measures of CRF were performed. Participants completed a 1 mile (1.6 km) long run to measure CRF. A generalised equation for the prediction of the VO_2 peak from the 1-mile run/walk performance in youth was used to convert the time taken on the 1.6 km run to a VO_2 peak uptake [301]. A sub-sample of participants aged 9, 12 and 15 years (n=2,595) completed a bicycle ergometer test of CRF from physical working capacity at a heart rate of 170 beats per minute (PWC_{170}) following a standardised procedure [302]. PWC_{170} has been previously shown to be highly correlated with peak oxygen consumption (VO_{2max}) (r=0.83) [267]. Absolute PWC_{170} was adjusted for lean body mass in the present study to provide a measure that was uncorrelated with lean body mass [220], as the absolute work load achieved is a function of muscle mass [183]. Childhood lean body mass was calculated using weight (kg) and estimates of percentage body fat derived from the sum of skinfolds. Triceps, biceps, subscapular and suprailiac skinfolds were measured to the nearest 0.1 mm using Holtain calipers (Holtain, Crymych, UK). Body density was calculated from the log of the sum of four skinfolds using age-specific regression equations [303] and fat percentage was determined. Lean body mass was then calculated by subtracting fat mass from total body mass.

7.2.3. *Follow-up alcohol consumption and alcohol use disorders measures*

We collected information about alcohol consumption from an FFQ at CDAH-1 in 2004–2006 when participants were aged 26–36 years old. Each participant reported their frequency of intake (options: never or <1/month, 1–3 times/month, once/week, 2–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–5 times/day, and >6 times/day) of alcoholic beverages (options: light, medium or full strength beer; red, white and sparkling wine; wine

cooler; spirits/liqueurs; spirit-based mixed drinks; sherry/port and other) over the last 12 months. The estimated amount of alcohol consumed per day for each type of beverage was determined by multiplying the frequency of drinking by the estimated grams of alcohol for each beverage type [174]. Individuals were classified into five groups according to daily alcohol intake: 0 drinks/day (Non-drinkers), >0-1 drink/day (Light drinkers), >1-2 drinks/day (Moderate drinkers), >2-3 drinks/day (Heavy drinkers) and >3 drinks/day (Very heavy drinkers), based on Australian guidelines [14].

At the follow-up, 2,170 participants had a 12-month DSM-IV-based AUDs diagnosis (e.g. alcohol dependence and/or alcohol abuse) by the CIDI [205].

7.2.4. Covariates

The following covariates were considered: sex, age, SES quartile based on the area of residence (high, medium-high, medium-low or low), school type (state, Catholic or independent), scholastic levels (excellent, above average, average, below average or poor), alcohol consumption in childhood (ever drinking vs never drinking) (childhood covariates), and history of lifetime leisure activity over three age periods: 15–19, 20–24 and 25–29 years. Historical Leisure Activity Questionnaires were administered, and then average mins/week in total lifetime physical activity including activities with friends, organised team, group, club or for school at each period were calculated, and personality traits in adulthood considered (NEO five-factor inventory: extraversion, neuroticism, conscientiousness, openness and agreeableness) [283].

7.2.5. Statistical analysis

Multivariable log binomial regression and linear regression were used for dichotomous or continuous outcomes, respectively. The coefficient (β) for the difference in alcohol consumption by g/day or RRs of dichotomous AUDs and 95% CIs in adulthood quantified the effects of childhood sport, physical activity and fitness at the baseline. We handled missing data from the baseline to the follow-up using a combination of IPW and MI [231]. MI applying chained equations with 50 estimations was used to replace missing data on covariates. The non-missing variables used for imputations were sex, age and type of school at the baseline in 1985. Weights for IPW were based on the inverse of the probability of providing baseline data given variables from 1985 (age, sex, smoking, SES quartile, type of

school, father's education, mother's education and scholastic level assigned by school). All statistical analyses were performed in Stata software program, version 15.0.

7.3. Results

The mean age of the 2,239 participants was 32.3 years at follow-up, with an average follow-up duration of 19.6 (SD: 0.6) years (Table 7-1 and Table 7-2).

Table 7-1. Characteristics of participants at baseline

Characteristics in childhood (9-15 years old)	**Total participants (N=2,239)**	
	n	**% or Mean (S.D.)**
Age, years	2,239	12.0 (2.0)
Ever drinking	729	33
Physical activity		
Total weekly PA (min/week)	2,239	435 (408)
School PE (min/week)	1,630	100 (95)
School PA (min/week)	1,963	166 (155)
Non-school PA (min/week)	2,004	323 (377)
School sport (min/week)	1,306	125 (135)
Discretionary sport (min/week)	2,014	344 (384)
Transport PA (min/week)	1,252	93 (115)
Past year sport, n (%)		
≤One	590	26
Two	617	28
≥Three	1,031	46
Team sport, n (%)		
≤One	1,334	60
Two	605	27
≥Three	300	13
Other sport, n (%)		
≤One	1,495	67

Two	466	21
≥Three	278	12
Fitness (Mean, ±SD)		
CRF, VO_2 max from 1.6km long run	2,638	47.5 (4.8)
CRF, PWC_{170} (W)	904	1.0 (20.3)
SES quartile		
Low	168	168 (8)
Medium-low	825	825 (38)
Medium-high	630	630 (29)
High	573	573 (26)
Scholastic level, n (%)		
Poor	40	40 (2)
Below average	248	248 (12)
Average	856	856 (41)
Above average	706	706 (34)
Excellent	254	254 (12)

Abbreviation: PA=physical activity; CRF=cardiorespiratory fitness; VO_2 max=peak oxygen uptake; PWC_{170}=physical work capacity at a heart rate 170 beat per minute.

Table 7-2. Characteristics of participants at follow-up

Characteristics in adulthood (26-36 years old)	**Total participants (N=2,239)**	
	n	**% or Mean (S.D.)**
Female	1,227	55
Age, years	2,239	32.3 (2.1)
Alcohol consumption status		
Non-drinkers (0 drinks/day)	352	15
Light drinkers (>0-1 drink/day)	1,181	53
Moderate drinkers (>1-2 drinks/day)	464	21
Heavy drinkers (>2-3 drinks/day)	117	5
Very heavy drinkers (>3 drinks/day)	125	6
Alcohol use disorder, positive	209	12
Alcohol dependence, positive	138	8
Education, n (%)		
Tertiary	885	40
Vocational	695	31
School only	658	29
Marital status		
Married/living as married	1,636	73
Single	524	23
Divorced/separated/widowed	79	4
Area of residence		
Major city	416	19
Inner regional	1,587	71
Outer regional/remote	229	10

7.3.1. Childhood physical activity, sport participation, cardiorespiratory fitness and adult alcohol consumption

Longitudinal associations between childhood physical activity, sport participation, CRF and alcohol consumption in adulthood are shown in Table 7-3 to Table 7-5. Participants with higher levels of total weekly physical activity in childhood had significantly higher total alcohol consumption per day, on average, in adulthood. Non-school physical activity in childhood was positively associated with adulthood alcohol consumption per day. The results persisted after adjusting for covariates identified via purposeful model building that included sex, age, SES and alcohol consumption in childhood, as well as personality in adulthood (Table 7-3).

Table 7-3. Multivariable linear regression on the association between childhood domain-specific physical activities and total alcohol consumption in early adulthood

	Unadjusted		Model 1		Model 2	
N=2,239	β (95% CI) †	P-value	β (95% CI) †	*P*-value	β (95% CI) †	*P-value*
Total weekly PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.45 (0.05, 2.85)	<0.05	1.30 (0.08, 2.68)	<0.05	1.32 (0.05, 2.71)	<0.05
Top third	3.16 (1.76, 4.56)	<0.001	2.59 (1.19, 3.99)	<0.001	2.50 (1.10, 3.89)	<0.001
P-trend		*<0.001*		*<0.001*		*<0.01*
Transport PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	-0.35 (-2.27, 1.57)	0.719	-0.54 (-2.43, 1.35)	0.573	-0.62 (-2.52, 1.28)	0.524
Top third	-1.53 (-3.56, 0.50)	0.140	-1.17 (-3.18, 0.84)	0.255	-1.42 (-3.44, 0.60)	0.599
P-trend		*0.155*		*0.250*		*0.167*
School sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.37 (-0.40, 3.15)	0.129	1.13 (-0.62, 2.89)	0.205	1.65 (-0.11, 3.40)	0.066
Top third	0.52 (-1.33, 2.38)	0.582	0.17 (-1.67, 2.02)	0.853	0.24 (-1.59, 2.08)	0.793

P-trend		*0.491*		*0.760*		*0.667*
School PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	-0.22 (-1.74, 1.29)	0.773	-0.28 (-1.79, 1.22)	0.712	-0.31 (-1.81, 1.20)	0.690
Top third	1.05 (-0.45, 2.54)	0.170	0.86 (-0.66, 2.38)	0.267	0.80 (-0.72, 2.32)	0.301
P-trend		*0.170*		*0.261*		*0.294*
Non-school PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.58 (-0.92, 2.07)	0.449	0.40 (-1.07, 1.87)	0.593	0.29 (-1.19, 1.78)	0.698
Top third	1.39 (-0.12, 2.91)	0.071	0.69 (-0.82, 2.19)	0.370	0.63 (-0.89, 2.15)	0.414
P-trend		*0.072*		*0.369*		*0.414*
School PE						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.98 (-0.66, 2.61)	0.241	1.00 (-0.82, 2.82)	0.281	1.23 (-0.59, 3.05)	0.186
Top third	0.52 (-1.08, 2.13)	0.523	0.28 (-1.51, 2.07)	0.760	0.12 (-1.67, 1.89)	0.905
P-trend		*0.469*		*0.814*		*0.984*

† β=beta coefficients expressed in unit change of grams of alcohol consumption per day

Abbreviation: CI=confidence interval; PA=physical activity; PE=physical education

† Model 1 adjusted for age, sex, SES quartiles, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

Discretionary sports, extra-curricular sports, combined team and individual sports, and the number of sports played in the last year in childhood were associated with greater daily alcohol consumption in adulthood. These associations persisted after adjusting for potential covariates which included age, sex, SES, alcohol consumption in childhood and personality traits in adulthood. Those who participated in team sports compared to those who did not participate in team sports in childhood also had higher alcohol consumption in adulthood; however, this result did not persist after adjusting for sex, age, SES, alcohol consumption in childhood and personality traits in adulthood (Table 7-4).

Table 7-4. Multivariable linear regression on the association between childhood sport participation and total alcohol consumption in early adulthood

	Unadjusted		Model 1		Model 2	
N=2,239	β (95% CI) †	P-value	β (95% CI) †	*P*-value	β (95% CI) †	*P-value*
Discretionary sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.94 (-0.53, 2.41)	0.211	0.64 (-0.81, 2.09)	0.389	0.70 (-0.76, 2.15)	0.347
Top third	2.05 (0.53, 3.57)	<0.01	1.25 (-0.26, 2.76)	0.106	1.37 (-0.14, 2.88)	0.075
P-trend		*<0.01*		*0.105*		*0.075*
Extra sport						
Bottom third	Ref.		Ref,		Ref,	
Middle third	1.64 (0.21, 3.07)	<0.05	1.43 (0.03, 2.83)	<0.05	1.35 (0.02, 2.77)	<0.05
Top third	2.86 (1.47, 4.26)	<0.001	2.55 (1.17, 3.92)	<0.001	2.58 (1.19, 3.98)	<0.001
P-trend		*<0.001*		*<0.001*		*<0.001*
Past year sport						
≤One	Ref.		Ref.		Ref.	
Two	2.18 (0.66, 3.71)	<0.01	1.86 (0.36, 3.35)	<0.05	2.04 (0.51, 3.58)	<0.01
≥Three	3.35 (1.99, 4.71)	<0.001	2.92 (1.59, 4.27)	<0.001	3.02 (1.65, 4.40)	<0.001
P-trend		*<0.001*		*<0.001*		*<0.001*
Team sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.63 (0.32, 2.95)	<0.05	0.75 (-0.56, 2.05)	0.262	0.87 (-0.45, 2.19)	0.196
Top third	2.47 (0.75, 4.20)	<0.01	0.94 (-0.78, 2.67)	0.282	0.94 (-0.81, 2.68)	0.292
P-trend		*<0.01*		*0.183*		*0.168*
Other sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.42 (-0.96, 1.79)	0.552	0.70 (-0.65, 2.05)	0.307	0.63 (-0.74, 2.01)	0.367
Top third	2.20 (0.82, 3.59)	<0.01	2.96 (1.60, 4.33)	<0.001	2.93 (1.53, 4.33)	<0.001

P-trend		*<0.01*		*<0.001*		*<0.001*
Combined sport						
None	Ref.		Ref.		Ref.	
Team only	0.92 (-1.38, 3.22)	0.432	0.18 (-2.08, 2.45)	0.874	0.02 (-2.49, 2.53)	0.988
Other only	0.35 (-2.12, 2.81)	0.782	0.79 (-1.64, 3.22)	0.523	0.58 (-2.08, 3.24)	0.670
Combined	2.52 (0.35, 4.69)	<0.05	2.29 (0.17, 4.42)	<0.05	2.12 (0.01, 4.51)	<0.05
P-trend		*<0.01*		*<0.01*		*<0.01*

† β=beta coefficients expressed in unit change of grams of alcohol consumption per day; † Model 1 adjusted for age, sex, SES quartiles, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

Participants with higher CRF measured based on the 1.6 km run in childhood had significantly greater levels of daily alcohol consumption in adulthood (Table 7-5). A similar result was observed for the subgroup where CRF was measured with PWC_{170} where CRF in childhood was associated with greater daily alcohol consumption in adulthood; however, the association was not statistically significant (Table 7-5).

Table 7-5. Multivariable linear regression on the association between childhood cardiorespiratory fitness based on 1.6km long run or PWC170 and total alcohol consumption in early adulthood

	Unadjusted		Model 1		Model 2	
	β (95% CI) †	P-value	β (95% CI) †	*P*-value	β (95% CI) †	*P-value*
VO_2 max from long run 1.6km (N=2,638)						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.65 (0.39, 2.92)	<0.05	0.62 (0.02, 1.80)	<0.05	0.26 (0.04, 1.75)	<0.05
Top third	5.64 (4.37, 6.92)	<0.001	2.60 (0.18, 1.70)	<0.01	2.50 (0.65, 4.36)	<0.01
P-trend		*<0.001*		*<0.05*		*<0.05*
CRF, PWC_{170} (W) (N=904)						
Bottom third	Ref.		Ref.		Ref.	
Middle third	2.08 (1.20, 3.57)	<0.01	2.29 (1.76, 5.48)	<0.01	3.07 (2.00, 5.83)	<0.01
Top third	1.67 (0.97, 2.84)	0.062	3.54 (1.44, 5.70)	<0.001	4.09 (1.81, 5.26)	<0.001
P-trend		*0.096*		<0.01		*<0.01*

† β=beta coefficients expressed in unit change of grams of alcohol consumption per day; W=Watt; * Child variables for weights were from the 1985 baseline survey of 9 to 15 years old and included age, sex, SES quartile, scholastic level, school type, mother education, father education. See methods for details; † Model 1 adjusted for sex, age, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

All results were consistent when applying combined MIs and IPW to manage loss to follow-up from baseline (Appendix Table 7-9 to Table 7-11).

7.3.2. *Childhood physical activity, sport participation, cardiorespiratory fitness and adult alcohol use disorders*

Longitudinal associations between childhood physical activity, sport participation, CRF and AUDs in adulthood are shown in Table 7-6 to Table 7-8. There was evidence of a reduced risk of AUDs in early adulthood with all childhood physical activity measures except school physical education; however, none of the associations were statistically significant (Table 7-6).

Table 7-6. Multivariable log-binomial regression on the association between childhood domain-specific physical activities and risk of being diagnosed as alcohol use disorders in early adulthood

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI) †	*P-value*
Total weekly PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.02 (0.76, 1.38)	0.879	1.01 (0.75, 1.36)	0.931	1.01 (0.75, 1.35)	*0.970*
Top third	0.91 (0.67, 1.24)	0.549	0.86 (0.63, 1.18)	0.354	0.85 (0.62, 1.17)	*0.312*
P-trend		*0.553*		*0.354*		*0.314*
Transport PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.95 (0.65, 1.39)	0.804	0.95 (0.65, 1.38)	0.780	0.94 (0.65, 1.36)	0.742
Top third	0.64 (0.39, 1.04)	0.073	0.70 (0.43, 1.13)	0.146	0.67 (0.41, 1.09)	0.103
P-trend		*0.094*		*0.173*		*0.124*
School PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.92 (0.67, 1.27)	0.628	0.96 (0.70, 1.31)	0.775	0.92 (0.67, 1.26)	0.594
Top third	0.79 (0.57, 1.10)	0.164	0.85 (0.61, 1.18)	0.330	0.82 (0.58, 1.15)	0.243
P-trend		*0.166*		*0.334*		*0.244*
Non-school PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.04 (0.76, 1.41)	0.816	1.01 (0.75, 1.37)	0.927	1.03 (0.76, 1.40)	0.837

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI) †	*P-value*
Top third	0.85 (0.61, 1.18)	0.328	0.79 (0.57, 1.09)	0.152	0.81 (0.58, 1.13)	0.219
P-trend		*0.347*		*0.161*		*0.232*
School PE						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.84 (0.58, 1.22)	0.360	0.93 (0.61, 1.40)	0.727	0.92 (0.60, 1.40)	0.699
Top third	1.09 (0.78, 1.53)	0.605	1.21 (0.83, 1.77)	0.320	1.15 (0.78, 1.70)	0.475
P-trend		*0.688*		*0.300*		*0.451*
School sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.33 (0.93, 1.91)	0.122	1.30 (0.90, 1.87)	0.161	1.28 (0.88, 1.86)	0.190
Top third	0.75 (0.47, 1.20)	0.233	0.77 (0.48, 1.23)	0.268	0.75 (0.47, 1.21)	0.239
P-trend		*0.405*		*0.427*		*0.385*

Abbreviation: CI=confidence interval; PA=physical activity; PE=physical education

†Model 1 adjusted for age, sex, SES quartiles, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

There was evidence of an increased risk of AUDs in early adulthood with all childhood sport participation measures, although none of the associations were statistically significant (Table 7-7).

Table 7-7. Multivariable log-binomial regression on the association between childhood sport participation and risk of being diagnosed as alcohol use disorders in early adulthood

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI) †	*P-value*
Discretionary sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.03 (0.76, 1.40)	0.857	0.95 (0.70, 1.29)	0.760	0.94 (0.69, 1.27)	0.669
Top third	0.95 (0.69, 1.31)	0.760	0.87 (0.63, 1.20)	0.380	0.88 (0.64, 1.22)	0.450
P-trend		*0.772*		*0.382*		*0.449*
Extra sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.03 (0.75, 1.41)	0.873	1.04 (0.76, 1.43)	0.798	0.98 (0.71, 1.35)	0.879
Top third	1.22 (0.91, 1.62)	0.184	1.21 (0.90, 1.61)	0.203	1.20 (0.90, 1.61)	0.211
P-trend		*0.207*		*0.219*		*0.256*
Past year sport						
≤One	Ref.		Ref.		Ref.	
Two	1.20 (0.85, 1.70)	0.303	1.18 (0.83, 1.66)	0.357	1.16 (0.81, 1.65)	0.420
≥Three	1.24 (0.91, 1.70)	0.178	1.23 (0.90, 1.68)	0.192	1.19 (0.86, 1.63)	0.299
P-trend		*0.198*		*0.207*		*0.325*
Team sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.23 (0.93, 1.63)	0.140	1.12 (0.85, 1.48)	0.427	1.07 (0.81, 1.42)	0.634
Top third	1.17 (0.72, 1.88)	0.530	1.04 (0.73, 1.49)	0.817	1.04 (0.72, 1.49)	0.843
P-trend		*0.106*		*0.637*		*0.739*
Other sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.02 (0.75, 1.39)	0.899	1.09 (0.80, 1.50)	0.603	1.02 (0.75, 1.40)	0.878

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI) †	*P-value*
Top third	1.09 (0.80, 1.47)	0.594	1.24 (0.92, 1.68)	0.156	1.22 (0.90, 1.66)	0.200
P-trend		*0.591*		*0.156*		*0.196*
Combined sport						
None	Ref.		Ref.		Ref.	
Team only	1.28 (0.74, 2.24)	0.378	1.18 (0.68, 2.05)	0.556	1.07 (0.58, 1.96)	0.829
Other only	1.14 (0.63, 2.08)	0.664	1.23 (0.68, 2.22)	0.499	1.11 (0.58, 2.12)	0.746
Combined	1.32 (0.78, 2.23)	0.301	1.35 (0.80, 2.26)	0.264	1.20 (0.67, 2.14)	0.538
P-trend		*0.419*		*0.195*		*0.359*

†Model 1 adjusted for age, sex, SES quartiles, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

Participants with higher CRF measured based on the 1.6 km run in childhood had a significantly higher risk of being diagnosed with an AUD in adulthood (Table 7-8). Compared to those in the bottom third of CRF measured by PWC_{170} in childhood, those in the middle third had significantly higher risk of being diagnosed with an AUD in adulthood (Table 7-8). Results persisted after adjusting for sex, SES, types of physical activity, sport participation, history of lifetime leisure activity over three age periods (15–19, 20–24 and 25–29 years) between childhood and adulthood, and personality traits in adulthood (Table 7-8).

Table 7-8. Multivariable log-binomial regression on the association between childhood cardiorespiratory fitness (CRF) and risk of being diagnosed as alcohol use disorders in early adulthood

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI)	*P*-value	RR (95% CI)	*P-value*
VO_2 max from long run 1.6km						
Bottom third	Ref.		Ref.		Ref.	
Middle third	2.10 (1.24, 3.58)	<0.01	2.28 (1.33, 3.90)	<0.01	2.36 (1.37, 4.05)	*<0.01*
Top third	1.69 (1.00, 2.87)	0.051	1.67 (0.97, 2.85)	0.063	1.65 (0.95, 2.85)	*0.073*
P-trend		*0.079*		0.112		*0.128*
CRF, PWC_{170} (W)						
Bottom third	Ref.		Ref.		Ref.	
Middle third	2.10 (1.24, 3.58)	<0.01	2.28 (1.33, 3.90)	<0.01	2.36 (1.37, 4.05)	*<0.01*
Top third	1.69 (1.00, 2.87)	0.051	1.67 (0.97, 2.85)	0.063	1.65 (0.95, 2.85)	*0.073*
P-trend		*0.079*		0.112		*0.128*

Abbreviation: CI=confidence interval; CRF=cardiorespiratory fitness; PWC170 (W)=physical work capacity at a heart rate of 170 bpm; W=Watt. Model 1 adjusted for age, sex, SES quartiles, types of PA, sport participation, alcohol consumption in childhood, history of lifetime leisure activity over three age periods 15-19, 20-24 and 25-29 years between childhood and adulthood; Model 2 adjusted for Model 1 + personality in adulthood

Applying combined MI and IPW did not substantially change the results (Appendix Table 7-12 to Table 7-14). Similar results were found after performing sensitivity analyses using alcohol dependence only (AUDs without alcohol abuse) as outcomes instead (Appendix Table 7-15 to Table 7-17).

7.4. Discussion

The present study is one of the first to examine the longitudinal associations between a diverse range of childhood physical activities, CRF and alcohol consumption in adulthood. We found that total physical activity and sport participation in childhood were significantly associated with higher alcohol consumption, but not AUDs, 20 years later. We also found that non-school physical activity, discretionary sport but not school physical activity or school sport in childhood predict daily alcohol consumption in adulthood. CRF measured based on the 1.6 km run and PWC_{170} in childhood predicted the likelihood to be diagnosed with an AUD in adulthood. These significant associations persisted after the adjustment for potential covariates in childhood and adulthood, demonstrating longitudinal links between childhood physical activity, particularly sport participation outside schools and alcohol consumption in adulthood.

Childhood total physical activity and sport participation were positively associated with adult alcohol consumption. The findings are consistent with other studies that have suggested a positive relationship between alcohol use and physical activity among adults [89]. Of domain-specific physical activity, childhood participation in sports in the past year, non-school physical activity and extra-curricular sports predicted adult total daily alcohol consumption. These associations might exist due to these environments fostering alcohol consumption as they may have been less structured than school activities. Those engaged in greater levels of physical activity and more sports in their leisure time during their school years may continue these habits into adolescence and adulthood, which then exposed them to environments that encouraged alcohol consumption. An important point to consider is that these sports were played in the 1980s when the social and cultural environments in such clubs were quite different to those that exist today. Another mechanism through which these types of sports might foster alcohol consumption is through links with corporate sponsorship, which remains relevant in contemporary settings. Recent findings have revealed a positive association between alcohol sports sponsorship and increased drinking among school children [304]. In this study, findings suggested that owning alcohol-branded merchandise associated with popular sports in Australia (e.g. cricket, rugby, motor racing) was associated with higher alcohol consumption [304]. Our results regarding sports support recent findings on the association between higher levels of risky alcohol consumption in community sports clubs compared to the general community in Australia in several team sports, including Australian football and cricket, but not individual sports [305]. Drinking alcohol socially with team

mates may be perceived to promote team work, social integration, entertainment or friendships as motivational aspects of participation [306, 307]. Others have also proposed that physically active people may perceive that occasional alcohol consumption is not detrimental to their health [308]. Our study provides novel longitudinal evidence of the associations between physical activity, sports and alcohol consumption.

It was unexpected that markers of CRF in childhood were associated with a higher risk of AUDs in adulthood. Based on previous findings [75, 86, 87], we hypothesised that greater CRF in childhood would 'protect' against adulthood AUDs. It is unlikely that the association between childhood CRF and adulthood AUDs is causal. Rather it is likely that childhood fitness is predictive of physical activity including sport participation across the life course. In turn, as discussed above, we hypothesise that it is the environment associated with sports participation that predicts adulthood alcohol consumption and, in a small group, development of AUDs. In support of this hypothesis, we found that childhood CRF measures were significantly but weakly related to childhood total physical activity, numbers of sports participated outside school and sports participation over three age periods (15–19, 20–24 and 25–29 years). However, adjustment for physical activity and sport participation over these age periods did not influence the association between childhood CRF and adulthood AUDs. In the present study, by further adjustments for self-rated physical activity and scholastic level in childhood, the results persisted, suggesting that these factors did not influence the association. A potential explanation for this finding is residual confounding despite the fact that we had information on a very wide range of potential confounding factors. Potentially important confounding factors that are associated with a higher risk of AUDs that we did not have include childhood psychiatric problems, trauma or genetic factors [309]. Studies that account for a wider range of potential explanatory variables are required to understand the nature of the association between CRF in childhood and AUDs in adulthood.

Previous research has hypothesised that personality may explain links between physical activity, fitness and alcohol consumption. This is because personality traits are predictive of physical activity [310, 311] and the risk of AUDs [312, 313]. We found that the personality traits of extraversion, openness, and agreeableness in adulthood were positively associated with sport participation in childhood and AUDs. However, even after adjusting for personality factors in adulthood, the association between childhood CRF and adulthood AUDs persisted. These analyses suggest that while personality factors are associated with CRF and AUDs they do not readily explain their links.

While we found statistically significant differences in the level of alcohol consumption based on several childhood measures of physical activity, the absolute differences in the levels of alcohol consumption were quite small but still of potential clinical significance. For example, participants with total weekly physical activity in the middle and highest thirds in childhood drank 2 to 3 g more of pure alcohol per day (which is equivalent to 1.5 to 2 standard drinks per week) in adulthood more than children in the lowest third of physical activity. This extra amount of consumption per week may not have immediate effects on the health on younger people but accumulated over time throughout adulthood it might have adverse health effects [52, 53, 314].

These findings have implications for understanding the complex association between alcohol consumption and health outcomes later in life. Recent studies have suggested that the direct benefits of alcohol consumption on a range of health outcomes have been over-stated [80]. The current results support these findings as they show a strong relationship between participation in physical activity and alcohol consumption over the life course. The dynamic nature of this association may be difficult to control for in longitudinal cohort studies that begin measuring people in adulthood. Inadequate control for the levels of physical activity across the life course, which likely have cumulative benefits for health [300], in those that consume alcohol might have contributed to the conflicting results regarding the health effects of alcohol.

The mostly anecdotal evidence around drinking and sports clubs has led to interventions to tackle risky alcohol consumption in sport [315, 316]. In Australia the ‘Good Sports’ intervention in community sports clubs was specifically created to address the potentially unhealthy links between alcohol and sporting clubs in the community [317].

The strengths of our study include the use of 20-year prospective data from childhood to adulthood, with objective measures of CRF. We considered a wide range of domain-specific physical activities and sport participation (including team sports versus other sports) in childhood. We were able to control for a range of potential confounding factors. We also examined the insights into the specific physical activity behaviours, including a range of sports participated and CRF, and objective measures of physical activity that might best predict alcohol consumption in adulthood.

The limitations of the study include the modest retention of participants from the original cohort (ASHFS), representing only 27% of the original participants in the ASHFS, which may

affect the generalisability of our findings to other populations. However, a comparison of the CDAH sample with population data for Australian adults aged 25–34 years showed that the proportion of participants who were current drinkers in adulthood was very similar to that in the general population [47]. Furthermore, the sensitivity analysis showed small differences after applying combined MI and IPM from the adulthood and childhood data to deal with failure to follow-up. Thus, the failure to follow-up did not appear to have had a great effect on the results. Other limitations also included the use of a questionnaire in childhood for self-report and pedometers or accelerometers. We did not have potential confounders for AUDs such as trauma or psychosocial adversity or genetic factors. We used a 12-month FFQ when a dedicated QF questionnaire might have been better.

7.5. Conclusions

The present study provides a better understanding of how physical activity, sport participation and CRF in early life are associated with alcohol consumption in young adults. A culture of drinking associated with sports may be related to these associations; however, we did not find strong evidence that team sports were worse for alcohol consumption than individual sports. The close links between alcohol and physical activity must be acknowledged when examining the potential casual links between alcohol and health outcomes.

Appendix 7. Additional Tables and Figures

Table 7-9. Multivariable linear regression with applying multiple imputation and inverse probability weighting* combined on the association between childhood domain-specific physical activities and total alcohol consumption in early adulthood

	Unadjusted		Model 1		Model 2	
N=2,239	β (95% CI) †	P-value	β (95% CI) †	*P*-value	β (95% CI) †	*P-value*
Total weekly PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.20 (0.37, 2.01)	<0.01	0.73 (0.17, 1.29)	<0.05	0.72 (0.15, 1.29)	<0.05
Top third	2.57 (1.63, 3.52)	<0.001	1.39 (0.73, 2.04)	<0.001	1.10 (0.46, 1.74)	<0.01
P-trend		*<0.001*		*<0.001*		*<0.01*
Transport PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.51 (-0.69, 1.71)	0.407	0.15 (-0.70, 1.01)	0.725	0.22 (-0.65, 1.10)	0.615
Top third	-0.36 (-1.53, 0.81)	0.549	-0.26 (-1.14, 0.62)	0.566	-0.27 (-1.16, 0.63)	0.560
P-trend		*0.707*		*0.646*		*0.662*
School sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.60 (-0.51, 1.71)	0.292	0.63 (-0.17, 1.44)	0.124	0.50 (-0.30, 1.31)	0.219
Top third	0.40 (-0.71, 1.52)	0.478	0.09 (-0.67, 0.86)	0.809	0.08 (-0.69, 0.85)	0.837
P-trend		*0.423*		*0.665*		*0.719*
School PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.07 (-0.81, 0.96)	0.872	-0.07 (-0.70, 0.56)	0.820	-0.15 (-0.78, 0.49)	0.649
Top third	0.50 (-0.42, 1.41)	0.289	0.14 (-0.52, 0.80)	0.673	0.07 (-0.60, 0.73)	0.847
P-trend		*0.305*		*0.686*		*0.861*
Non-school PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.80 (-0.06, 1.65)	0.069	0.44 (-0.17, 1.05)	0.161	0.39 (-0.20, 0.98)	0.194

Top third	1.30 (0.37, 2.21)	<0.01	0.68 (0.02, 1.34)	<0.05	0.66 (0.03, 1.28)	<0.05
P-trend		*<0.05*		*<0.05*		*<0.05*
School PE						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.03 (-0.99, 1.06)	0.948	0.10 (-0.74, 0.96)	0.806	0.08 (-0.77, 0.94)	0.849
Top third	-0.15 (-1.14, 0.84)	0.773	-0.39 (-1.13, 0.35)	0.303	-0.42 (-1.15, 0.31)	0.261
P-trend		0.797		*0.293*		*0.251*

† β=beta coefficients expressed in unit change of grams of alcohol consumption per day

Abbreviation: CI=confidence interval; PA=physical activity; PE=physical education

* Child variables for weights were from the 1985 baseline survey of 9 to 15 years old and included age, sex, SES quartile, scholastic level, school type, mother education, father education. See methods for details.

† Model 1 adjusted for age, sex, SES quartiles; Model 2 adjusted for Model 1 + personality

Table 7-10. Multivariable linear regression with applying multiple imputation and inverse probability weighting* combined on the association between childhood sport participation and total alcohol consumption in early adulthood

	Unadjusted		Model 1		Model 2	
N=2,239	β (95% CI) †	P-value	β (95% CI) †	*P*-value	β (95% CI) †	*P-value*
Discretionary sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.01 (0.11, 1.80)	<0.05	0.56 (-0.04, 1.15)	0.069	0.53 (-0.08, 1.14)	0.088
Top third	1.76 (0.73, 2.42)	<0.01	0.84 (0.18, 1.36)	<0.05	0.60 (0.15, 1.25)	<0.05
P-trend		*<0.05*		*<0.05*		*<0.05*
Extra sport						
Bottom third	Ref.		Ref,		Ref,	
Middle third	1.01 (0.12, 1.82)	<0.05	0.51 (-0.08, 1.10)	0.087	0.50 (-0.10, 1.09)	0.101
Top third	2.16 (1.12, 3.10)	<0.001	1.42 (0.69, 2.15)	<0.001	1.28 (0.56, 2.00	<0.001
P-trend		*<0.001*		*<0.001*		*<0.001*
Past year sport						
≤One	Ref.		Ref.		Ref.	
Two	1.29 (0.47, 2.11)	<0.01	0.84 (0.24, 1.43)	<0.01	0.74 (0.13, 1.35)	<0.05
≥Three	2.22 (1.39, 2.90)	<0.001	1.35 (0.78, 1.92)	<0.001	1.23 (0.66, 1.81)	<0.001
P-trend		*<0.001*		*<0.001*		*<0.001*
Team sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.23 (0.42, 2.05)	<0.01	0.49 (-0.08, 1.06)	0.090	0.45 (-0.12, 1.02)	0.125
Top third	1.54 (0.38, 2.69)	<0.01	0.40 (-0.38, 1.18)	0.313	0.31 (-0.47, 1.09)	0.430
P-trend		*<0.01*		*0.137*		*0.214*
Other sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.26 (-0.50, 1.01)	0.509	0.17 (-0.34, 0.68)	0.512	0.11 (-0.41, 0.63)	0.672

	Unadjusted		Model 1		Model 2	
N=2,239	β (95% CI) †	P-value	β (95% CI) †	*P*-value	β (95% CI) †	*P-value*
Top third	1.69 (0.84, 2.54)	<0.001	1.48 (0.83, 2.12)	<0.001	1.38 (0.74, 2.03)	<0.001
P-trend		*<0.001*		*<0.001*		*<0.001*
Combined sport						
None	Ref.		Ref.		Ref.	
Team only	0.82 (-0.31, 1.96)	0.156	0.23 (-0.64, 1.10)	0.603	0.23 (-0.66, 1.12)	0.616
Other only	0.60 (-0.62, 1.81)	0.335	0.52 (-0.45, 1.50)	0.294	0.53 (-0.46, 1.52)	0.296
Combined	1.87 (0.78, 2.95)	<0.01	1.09 (0.22, 1.95)	<0.05	0.98 (0.09, 1.86)	<0.05
P-trend		*<0.01*		*<0.01*		*<0.01*

† β=beta coefficients expressed in unit change of grams of alcohol consumption per day

* Child variables for weights were from the 1985 baseline survey of 9 to 15 years old and included age, sex, SES quartile, scholastic level, school type, mother education, father education. See methods for details.

† Model 1 adjusted for age, sex, SES quartiles; Model 2 adjusted for Model 1 + personality

Table 7-11. Multivariable linear regression with applying multiple imputation and inverse probability weighting* combined on the association between childhood cardiorespiratory fitness based on peak oxygen uptake (VO_2 max) from 1.6km long run performance and based on a bicycle ergometer test at a heart rate of 170 beats per minute and total alcohol consumption in early adulthood

	Unadjusted		Model 1		Model 2	
	β (95% CI) †	P-value	β (95% CI) †	*P*-value	β (95% CI) †	*P-value*
VO_2 max from long run 1.6km (N=2,638)						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.37 (0.74, 2.00)	<0.001	0.62 (0.07, 1.18)	<0.05	0.60 (0.04, 1.15)	<0.05
Top third	3.88 (3.07, 4.70)	<0.001	0.94 (0.18, 1.70)	<0.05	0.88 (0.13, 1.63)	<0.05
P-trend		*<0.001*		*<0.05*		*<0.05*
CRF, PWC_{170} (W) (N=904)						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.73 (-0.74, 2.19)	0.331	0.68 (-0.37, 1.74)	0.205	0.62 (-0.45, 1.69)	0.258
Top third	1.11 (-0.32, 2.53)	0.129	0.65 (-0.37, 1.66)	0.211	0.57 (-0.46, 1.60)	0.281
P-trend		*0.148*		*0.235*		*0.305*

† β=beta coefficients expressed in unit change of grams of alcohol consumption per day; W=Watt. * Child variables for weights were from the 1985 baseline survey of 9 to 15 years old and included age, sex, SES quartile, scholastic level, school type, mother education, father education. See methods for details.

† Model 1 adjusted for sex, age; Model 2 adjusted for Model 1 + personality

Table 7-12. Multivariable log-binomial regression with applying multiple imputation and inverse probability weighting* combined on the association between childhood domain-specific physical activities and early adulthood alcohol use disorders

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI)	*P-value*
Total weekly PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.06 (0.73, 1.53)	0.771	1.03 (0.70, 1.51)	0.883	1.03 (0.56, 1.91)	0.922
Top third	0.91 (0.62, 1.33)	0.549	0.86 (0.58, 1.28)	0.461	0.98 (0.54, 1.76)	0.937
P-trend		*0.628*		*0.474*		*0.941*
Transport PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.15 (0.70, 1.88)	0.575	1.09 (0.66, 1.80)	0.737	1.42 (0.62, 3.23)	0.408
Top third	0.79 (0.43, 1.43)	0.433	0.81 (0.43, 1.50)	0.502	1.06 (0.36, 3.17)	0.912
P-trend		*0.553*		*0.601*		*0.767*
School sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.26 (0.80, 1.98)	0.321	1.23 (0.77, 1.99)	0.387	1.24 (0.58, 2.63)	0.576
Top third	0.75 (0.43, 1.31)	0.317	0.77 (0.43, 1.38)	0.383	0.53 (0.21, 1.34)	0.177
P-trend		*0.445*		*0.511*		*0.243*
School PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.98 (0.66, 1.46)	0.917	0.92 (0.61, 1.39)	0.696	0.94 (0.49, 1.81)	0.852
Top third	0.80 (0.53, 1.20)	0.278	0.83 (0.54, 1.27)	0.382	1.07 (0.55, 2.08)	0.836
P-trend		*0.286*		*0.384*		*0.850*
Non-school PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.06 (0.72, 1.56)	0.782	1.06 (0.71, 1.58)	0.769	1.22 (0.65, 2.31)	0.535
Top third	0.84 (0.56, 1.27)	0.412	0.81 (0.53, 1.25)	0.344	0.95 (0.50, 1.83)	0.888
P-trend		*0.419*		*0.532*		*0.911*

School PE						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.80 (0.51, 1.26)	0.329	0.88 (0.53, 1.46)	0.616	1.17 (0.55, 2.50)	0.687
Top third	1.09 (0.72, 1.66)	0.674	1.18 (0.71, 1.95)	0.520	1.15 (0.54, 2.46)	0.722
P-trend		*0.868*		*0.544*		*0.718*

Abbreviation: CI=confidence interval; PA=physical activity; PE=physical education

* Child variables for weights were from the 1985 baseline survey of 9 to 15 years old and included age, sex, SES quartile, scholastic level, school type, mother education, father education. See methods for details.

†Model 1 adjusted for age, sex, SES quartiles, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

Table 7-13. Multivariable log-binomial regression with applying multiple imputation and inverse probability weighting* combined on the association between childhood sport participation and early adulthood alcohol use disorders

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI)	*P-value*
Discretionary sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.89 (0.60, 1.32)	0.561	0.81 (0.54, 1.21)	*0.303*	0.84 (0.44, 1.60)	*0.586*
Top third	0.91 (0.61, 1.36)	0.655	0.87 (0.57, 1.32)	*0.504*	0.90 (0.48, 1.69)	*0.737*
P-trend		*0.653*		*0.481*		*0.718*
Extra sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.11 (0.75, 1.66)	0.603	1.03 (0.67, 1.53)	*0.940*	1.38 (0.76, 2.51)	*0.291*
Top third	1.10 (0.77, 1.58)	0.593	1.11 (0.80, 1.61)	*0.571*	1.16 (0.62, 2.15)	*0.640*
P-trend		*0.542*		*0.598*		*0.480*
Past year sport						
≤One	Ref.		Ref.		Ref.	
Two	1.16 (0.75, 1.77)	0.509	1.11 (0.71, 1.74)	*0.635*	1.37 (0.70, 2.71)	*0.359*
≥Three	1.19 (0.81, 1.75)	0.382	1.13 (0.75, 1.69)	*0.568*	1.51 (0.79, 2.90)	*0.568*
P-trend		*0.392*		*0.584*		*0.218*
Team sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.11 (0.79, 1.57)	0.546	0.93 (0.66, 1.32)	0.694	1.01 (0.58, 1.72)	0.990
Top third	1.21 (0.77, 1.91)	0.890	0.98 (0.61, 1.59)	0.943	1.51 (0.72, 3.17)	0.274
P-trend		*0.362*		*0.845*		*0.367*
Other sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.98 (0.67, 1.43)	0.910	0.94 (0.63, 1.39)	0.752	1.03 (0.57, 1.88)	0.911
Top third	1.03 (0.71, 1.50)	0.886	1.19 (0.81, 1.75)	0.385	1.31 (0.72, 2.40)	0.374

P-trend		*0.891*		*0.410*		*0.389*
Combined sport						
None	Ref.		Ref.		Ref.	
Team only	1.09 (0.55, 2.15)	0.804	0.85 (0.40, 1.81)	0.666	1.23 (0.36, 4.20)	0.739
Other only	0.90 (0.44, 1.87)	0.787	0.85 (0.38, 1.89)	0.686	1.34 (0.37, 4.83)	0.658
Combined	1.12 (0.59, 2.12)	0.726	0.94 (0.45, 1.93)	0.859	1.37 (0.42, 4.53)	0.604
P-trend		*0.724*		*0.796*		*0.560*

* Child variables for weights were from the 1985 baseline survey of 9 to 15 years old and included age, sex, SES quartile, scholastic level, school type, mother education, father education. See methods for details.

†Model 1 adjusted for age, sex, SES quartiles, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

Table 7-14. Multivariable log-binomial regression with applying multiple imputation and inverse probability weighting* combined on the association between childhood cardiorespiratory fitness (CRF) and risk of being diagnosed as alcohol use disorders in early adulthood

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI)	P-value
VO_2 max from long run 1.6km						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.52 (1.04, 2.23)	<0.05	1.24 (0.84, 1.85)	0.280	1.35 (0.90, 2.01)	0.145
Top third	2.68 (1.88, 3.83)	<0.001	1.67 (1.10, 2.52)	<0.05	1.83 (1.20, 2.81)	<0.01
P-trend		*<0.001*		*<0.05*		*<0.01*
CRF, PWC_{170} (W)						
Bottom third	Ref.		Ref.		Ref.	
Middle third	2.50 (1.25, 4.97)	<0.01	2.68 (1.31, 5.48)	<0.01	2.82 (1.34, 5.92)	*<0.01*
Top third	1.67 (0.86, 3.23)	0.129	1.59 (0.80, 3.16)	0.182	1.58 (0.77, 3.26)	*0.211*
P-trend		*0.149*		0.225		*0.252*

Abbreviation: CI=confidence interval; W=Watt

* Child variables for weights were from the 1985 baseline survey of 9 to 15 years old and included age, sex, SES quartile, scholastic level, school type, mother education, father education. See methods for details.

† Model 1 adjusted for age, sex, SES quartiles, types of PA, sport participation, alcohol consumption in childhood, history of lifetime leisure activity over three age periods 15-19, 20-24 and 25-29 years between childhood and adulthood; Model 2 adjusted for Model 1 + personality in adulthood

Table 7-15. Multivariable log-binomial regression on the association between childhood domain-specific physical activities and early adulthood alcohol dependence

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI)	*P-value*
Total weekly PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.96 (0.65, 1.42)	0.832	0.96 (0.64, 1.43)	0.883	0.93 (0.62, 1.37)	0.701
Top third	1.01 (0.68, 1.49)	0.969	0.94 (0.63, 1.40)	0.757	0.94 (0.64, 1.40)	0.774
P-trend		*0.408*		*0.757*		*0.773*
Transport PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.98 (0.62, 1.57)	0.938	0.96 (0.60, 1.54)	0.857	0.96 (0.64, 1.53)	0.854
Top third	0.62 (0.27, 1.00)	0.052	0.61 (0.28, 1.08)	0.081	0.66 (0.28, 1.10)	0.089
P-trend		*0.072*		*0.095*		*0.105*
School sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.49 (0.92, 2.42)	0.105	1.39 (0.84, 2.31)	0.303	1.38 (0.84, 2.26)	0.202
Top third	0.94 (0.52, 1.69)	0.833	0.90 (0.48, 1.66)	0.732	0.97 (0.52, 1.78)	0.910
P-trend		*0.975*		*0.879*		*0.920*
School PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.89 (0.59, 1.35)	0.582	0.89 (0.58, 1.35)	0.581	0.94 (0.62, 1.43)	0.772
Top third	0.75 (0.49, 1.15)	0.193	0.75 (0.48, 1.17)	0.201	0.80 (0.51, 1.24)	0.307
P-trend		*0.193*		*0.199*		*0.309*
Non-school PA						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.13 (0.76, 1.67)	0.559	1.13 (0.76, 1.69)	0.538	1.12 (0.76, 1.67)	0.565
Top third	0.90 (0.59, 1.37)	0.613	0.86 (0.55, 1.34)	0.504	0.87 (0.56, 1.34)	0.522
P-trend		*0.641*		*0.513*		*0.539*
School PE						

Bottom third	Ref.		Ref.		Ref.	
Middle third	0.94 (0.59, 1.49)	0.783	1.00 (0.58, 1.74)	0.991	1.01 (0.60, 1.71)	0.965
Top third	0.85 (0.53, 1.35)	0.478	0.80 (0.46, 1.40)	0.434	0.84 (0.49, 1.45)	0.533
P-trend		*0.480*		*0.422*		*0.529*

Abbreviation: CI=confidence interval; PA=physical activity; PE=physical education

†Model 1 adjusted for age, sex, SES quartiles, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

Table 7-16. Multivariable log-binomial regression on the association between childhood sport participation and early adulthood alcohol dependence

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI)	*P-value*
Discretionary sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.97 (0.65, 1.46)	0.893	0.89 (0.59, 1.34)	0.564	0.90 (0.50, 1.35)	0.595
Top third	1.05 (0.70, 1.58)	0.801	0.98 (0.65, 1.48)	0.931	1.01 (0.67, 1.52)	0.966
P-trend		*0.807*		*0.920*		*0.983*
Extra sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.18 (0.80, 1.76)	0.405	1.17 (0.78, 1.75)	0.940	1.23 (0.82, 1.83)	0.315
Top third	1.21 (0.83, 1.77)	0.322	1.22 (0.83, 1.80)	0.300	1.29 (0.88, 1.88)	0.199
P-trend		*0.287*		*0.272*		*0.170*
Past year sport						
≤One	Ref.		Ref.		Ref.	
Two	0.82 (0.52, 1.29)	0.389	0.83 (0.52, 1.33)	0.442	0.81 (0.51, 1.28)	0.363
≥Three	1.09 (0.75, 1.59)	0.660	1.09 (0.74, 1.61)	0.663	1.12 (0.76, 1.67)	0.561
P-trend		*0.524*		*0.529*		*0.420*
Team sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.22 (0.85, 1.74)	0.280	1.08 (0.75, 1.53)	0.685	1.11 (0.78, 1.56)	0.572
Top third	1.15 (0.72, 1.84)	0.553	0.96 (0.60, 1.55)	0.872	1.04 (0.64, 1.69)	0.885
P-trend		*0.362*		*0.988*		*0.737*
Other sport						
Bottom third	Ref.		Ref.		Ref.	
Middle third	0.83 (0.56, 1.24)	0.366	0.85 (0.57, 1.28)	0.443	0.87 (0.58, 1.31)	0.504
Top third	1.06 (0.73, 1.54)	0.762	1.23 (0.84, 1.81)	0.293	1.21 (0.82, 1.79)	0.328
P-trend		*0.748*		*0.300*		*0.330*

Combined sport						
None	Ref.		Ref.		Ref.	
Team only	1.07 (0.56, 2.04)	0.842	0.95 (0.46, 1.96)	0.886	1.01 (0.49, 2.05)	0.985
Other only	1.08 (0.54, 2.16)	0.818	1.13 (0.52, 2.46)	0.758	1.17 (0.54, 2.50)	0.694
Combined	0.97 (0.52, 1.78)	0.915	0.95 (0.47, 1.92)	0.877	1.00 (0.50, 2.01)	0.989
P-trend		*0.677*		*0.887*		*0.969*

†Model 1 adjusted for age, sex, SES quartiles, alcohol consumption in childhood; Model 2 adjusted for Model 1 + personality in adulthood

Table 7-17. Multivariable log-binomial regression on the association between childhood cardiorespiratory fitness (CRF) and risk of being diagnosed as alcohol dependence in early adulthood

	Unadjusted		Model 1		Model 2	
	RR (95% CI)	P-value	RR (95% CI) †	*P*-value	RR (95% CI)	P-value
VO_2 max from long run 1.6km						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.15 (0.75, 1.76)	0.532	1.50 (0.69, 3.26)	0.301	1.47 (0.66, 3.26)	0.349
Top third	1.99 (1.36, 2.91)	<0.001	2.78 (1.23, 6.29)	<0.05	3.02 (1.24, 7.36)	<0.05
P-trend		*<0.001*		*<0.05*		*<0.05*
CRF, PWC_{170} (W)						
Bottom third	Ref.		Ref.		Ref.	
Middle third	1.75 (0.91, 3.35)	0.092	3.09 (1.77, 6.08)	<0.01	3.63 (1.94, 6.37)	<0.01
Top third	1.74 (0.90, 3.37)	0.101	3.26 (1.42, 6.83)	<0.01	3.35 (1.78, 6.04)	<0.01
P-trend		*0.096*		<0.01		*<0.01*

Abbreviation: CI=confidence interval; W=Watt. † Model 1 adjusted for age, sex, SES quartiles, types of PA, sport participation, alcohol consumption in childhood, history of lifetime leisure activity over three age periods 15-19, 20-24 and 25-29 years between childhood and adulthood; Model 2 adjusted for Model 1 + personality in adulthood

Table 7-18. List of sports classified as team sports and other sports

Teams sports	Other sports
Australian Rules Football	Acrobatics
Baseball	Aerobics
Basketball	Archery
Cricket	Athletics
Football	Badminton
Hockey	Ballet
Ice hockey	Baton twirling
Indoor cricket	Bike riding
Korf ball	BMX
Lacrosse	Bush walking
Minkey	Calisthenics
Netball	Canoeing
Newcombe	Cross country
Rugby	Cycling
Rugby league	Dancing
Rugby union	Equestrian/Horse riding
Soccer	Golf
Softball	Gymnastics
Softcrosse	Ice skating
T ball	Jazz ballet
Touch football	Lazzercise

Teams sports	Other sports
Volleyball	Jogging
Long ball	Judo
Brack ball	Kanga cricket
Underwater hockey	Karate
Rowing	Life saving
Water polo	Martial arts
	Motor bike riding
	Orienteering
	Ping pong
	Physical culture
	Playground games
	Racqueball
	Rythmic gymnastics
	Roller skating
	Rounders
	Sailing
	Skiing
	Squash
	Swimming
	Tai chi
	Tennis
	Tenpin bowling

Teams sports	Other sports
	Trampolining
	Triathlons
	Water skiing
	Weights
	Yoga
	Surfing
	Skating
	Surf skiing
	Wind-surfing
	Skateboard
	Work around house/farm
	Marching
	Billy cart racing
	Fencing
	Wrestling
	Skin diving
	Fishing
	Snooker
	Go-karts
	Other sport
	Boxing

Chapter 8

Summary, implications, future directions and conclusions

8 Chapter 8. Summary, implications, future directions and conclusions

8.1. Summary of background

While it is well-established that excessive long-term use of alcohol has harmful effects on health, there has been debate on the relationship between light to moderate alcohol consumption and diseases, particularly cardio-metabolic diseases. When the research for this thesis began in 2015, there was evidence of potential health benefits of moderate alcohol consumption. Whether the associations were causal or due to confounding factors was uncertain. The CDAH study in Australia that measured alcohol consumption, health behaviours and outcomes over the life course offered an opportunity to further explore these associations in young, healthy adults. The thesis began with an examination of alcohol consumption and 'classic' cardiovascular risk factors in Chapter 3, followed by examination of patterns of alcohol consumption, total alcohol consumption and pre-clinical measures of cardiovascular and metabolic health in Chapter 4, analysis of alcohol consumption and novel biomarkers for cardiovascular health assessed with metabolomics analysis in Chapter 5, a detailed examination of childhood physical activity and fitness as predictors of alcohol consumption in adulthood was presented in Chapter 6, and longitudinal bidirectional associations between alcohol consumption and physical activity in adulthood were explored in Chapter 7.

8.2. Summary of results

Chapter 3 – Associations between alcohol consumption and cardio-metabolic risk factors in young adults

Alcohol consumption was very common in this cohort of young adults and the majority were light to moderate drinking (54% of drinking >0-10g/day and 22% of drinking >10-20 g/day) and average consumption of 9.9 grams per day. People consuming light to moderate amounts of alcohol also had a host of other concurrent healthy behaviours such as better diet quality, greater amounts of total physical activity, and a lower prevalence of depression and anxiety compared to their non-drinker or heavy drinker counterparts. I found that moderate alcohol consumption was associated with a lower prevalence of MetS when compared to light

drinkers but not favourable levels of other risk factors (e.g. lipids or BP) accounting for potential confounders, including physical activity, CRF and mental health. There were no apparent cardiovascular or metabolic health effects of having AUDs within the previous 12 months within this cohort of younger people. Beer and wine showed similar associations to total alcohol consumption with the risk factors examined.

Chapter 4 – Patterns of alcohol consumption, carotid intima-media thickness and insulin resistance in young adults

There were three patterns of alcohol consumption evident in this cohort: 'none/light' consumers (15.4%), 'moderate beer, wine and spirit' consumers (73.7%), and 'moderate-wine & heavy beer' consumers (10.8%). I compared whether these patterns, which combined frequency and types of consumption, were better at predicting pre-clinical cardiovascular risk factors than a simple combined summary of total alcohol consumption. I found that the most common way that younger people consume alcohol, moderate consumption of beer, wine and spirits, was not associated with cardiovascular or metabolic health benefits once a range of potential confounding factors was considered. Total alcohol consumption was significantly associated with lower prevalence of insulin resistance. Information on patterns of alcohol consumption did not provide greater utility than simply gathering information on frequency and quantity of alcohol in prediction of outcomes.

Chapter 5 – The metabolomics signatures of alcohol consumption in young adults

A diverse range of metabolomics signatures associated with benefits and harm to cardiovascular and metabolic health were found to be related to alcohol consumption. The results were mostly similar to the only other existing study in Finland that examined metabolic profiling and alcohol consumption in young adults. Exceptions were for associations with some triglycerides, FA and several low molecular weight metabolites. Limited differences were found in associations with metabolites among different types of beverages and all beverages combined. Including diet and CRF, but not mental health, appeared to influence the associations. These findings of positive and negative associations between alcohol and metabolic markers support recent findings on alcohol consumption differentially predicting CVDs such as myocardial infarction and stroke.

Chapter 6 – An examination of bidirectional associations between physical activity and alcohol consumption in adulthood: A 5-year cohort study

Longitudinal data showed that there were bidirectional associations between physical activity and alcohol consumption in a cohort of young adults over a 5-year period. Greater minutes of total physical activity per week at the baseline were found to be associated with the consumption of significantly more alcohol in adulthood. In contrast, people who drank more alcohol at the baseline were less likely to increase their physical activity over the 5 years of follow-up. Results were largely similar when the objective measure of steps per day measured by pedometer was used instead of self-reported physical activity by questionnaires.

Chapter 7 – Childhood physical activity and sport participation as predictors of early adulthood alcohol consumption and alcohol use disorders

Longitudinal data showed that childhood physical activity and sport participation were positively associated with adulthood alcohol consumption. Childhood CRF was also found to be associated with adulthood AUDs. Non-school physical activity and discretionary sport outside school but not school physical activity or school sport in childhood were associated with alcohol consumption in adulthood. These associations were independent of sex, SES, childhood psychological wellbeing, mental health, self-rated physical activity, scholastic level, history of lifetime leisure activity between childhood and adulthood and adulthood personality. The findings are consistent with other studies suggesting a positive relationship between alcohol use and physical activity of adults in the general population. The association between childhood CRF and adulthood AUDs was unexpected and unlikely to be causal. Potential explanations may include the greater exposure to environments that promote alcohol consumption among children that were fitter or other shared psychosocial factors such as motivation.

8.3. Strengths and limitations

This research has several strengths. Participants were from a large, nation-wide population-based cohort that were reasonably representative of the general population from which they were drawn at the baseline. There was an extensive range of study factors measured using standardised protocols including for AUDs, objective measures of physical activity, CRF and cardiovascular risk factors, together with metabolomic signatures. The study also included a host of potential mediators, effect modifiers and confounders of the association between alcohol and different outcomes. This allowed exploration of the possible mechanisms linking

alcohol to health behaviours and outcomes but also made the findings more likely to be free of confounding bias. The fact that the participants included in this research were young adults can also be considered a strength. Many studies of risk factors for cardiovascular risk factors have focused on adults at older age, with less information available for younger adults. However, this may also be considered as a limitation as the lack of associations between alcohol and some outcomes could be due to the fact that these people have not accumulated enough 'risk' associated with their alcohol consumption at their younger ages. Examining association between risk factors and outcomes across the life course is recognised as being important for understanding the mechanisms linking risk factors to outcomes and for understanding when the timing of interventions.

There are also several limitations. Cross-sectional analyses were used in three out of the five studies. This limits the causal inferences that can be drawn regarding the relationship between the exposures and outcomes of these studies. For example, there is the possibility of reverse causation whereby individuals with more adverse health risk factors may stop drinking alcohol to improve risk factor levels. When I began this research, the CDAH study had recently completed a questionnaire-based follow-up of participants; however, this did not include clinical measures. This meant that longitudinal analyses of the association between alcohol consumption and cardiovascular or metabolic risk factors could not be examined. Since then, the investigator team received funding to complete another follow-up with clinical measures that will be completed by mid-2019. The availability of this new follow-up data will enable longitudinal examination of the associations explored in this thesis.

There was considerable loss to follow-up in the CDAH study. This may have resulted in under or over estimation of associations if the association between the exposure and the outcome was different among participants and non-participants. This failure to follow-up might result in non-representative samples. It is particularly problematic when attempting to estimate the population prevalence of risk factors or outcomes. However, this research was an analytical investigation of associations between factors. We used a large population-based sample that was well characterised across the life course with a range of confounders, mediators and effect modifiers that were heterogenous. Threats to external validity are therefore less of an issue in these circumstances. Further, I explored possible effects of the attrition using IPW and sought to minimise loss of data through application of MI.

Unmeasured confounders may be another potential limitation of this research. As a study of general health and fitness in children in the 1980s the study did not have measures of some

strong risk factors for AUDs or heavier alcohol consumption in adults. This includes factors such as family background, trauma, and genetic factors. While the study had several validated methods for measuring physical activity, the current gold standard is to use accelerometers. Using these may have minimised measurement errors compared with using pedometers and a self-reported questionnaire. However, the high cost of accelerometers greatly reduces their feasibility in large population-based studies and they were not commonly used in large studies at the time of the 'baseline' adult assessment in 2004–2006. To enable comparisons over time, the investigator team have decided to continue to use pedometers.

An important point to consider is the changing nature of social and cultural attitudes and beliefs around alcohol consumption. For example, guidelines around alcohol in sporting clubs and in the community are different than the baseline in the 1980s. This may particularly affect the interpretation of the findings between childhood physical activity, sport participation and cardiorespiratory fitness and adulthood alcohol consumption. Recent changes in alcohol policy and interventions to tackle risky alcohol consumption in sport may mean these types of associations are less relevant now [315, 316]. However, in support of the relevance of these findings there are recent data showing that drinking in sports clubs is still common and that there is an association between advertising of alcohol during sports and drinking amongst school children [304]. Nonetheless, the possibility that the unhealthy links between alcohol and sporting clubs are different now can be examined more contemporary cohorts of children followed into adulthood.

The sample of the CDAH study examined in this thesis is of high SES and predominantly white, which may affect the generalizability of our findings to other populations. However, a comparison of the CDAH sample with population data for Australian adults aged 25-34 showed that the proportion of participants who were current drinkers in adulthood and other general characteristics were very similar to that in the general population [47]. Thus, these characteristics does not appear to have had a great effect on the generalizability of the findings in the Australian settings.

8.4. Implications and future directions

There were four key findings from the research that have implications for research and public health, as well as generating future directions for research.

8.4.1. Modest benefits of alcohol consumption for cardiovascular and metabolic health

When the research for this thesis was begun in 2015, there was considerable debate regarding the supposed benefits of alcohol consumption for health. There were clear links between very high or risky levels of alcohol consumption and a range of different diseases. However, there was also a large body of literature suggesting that moderate levels of consumption were associated with a lower risk of mortality and morbidity, particularly for CVDs [79, 80, 104, 108, 109]. In that body of research, low to moderate drinkers (usually defined as those drinking 10–20 g/day) appeared to have the lowest risks of several health outcomes compared to abstainers or heavier drinkers. There had been discussion among authors about concerns regarding selection bias, competing risks related to diseases occurring later in life [79], inappropriate selection of a reference group (particularly 'abstainer bias') and weak adjustment for confounders [104]. There were also limitations in that previous findings including that a large number of studies focused on men only [77, 112, 128, 133, 136, 142] and people who were middle-aged or older [112, 113, 125, 133-135, 137] where co-morbid diseases may make estimating associations difficult. Therefore, it was my objective to undertake a series of analyses to attempt to overcome these potential biases in this thesis.

The findings showed that there were very modest effects of light to moderate alcohol consumption on the major risk factors for CVDs once they were accounted for covariates, with some exceptions. These findings are complemented by recent publications including new epidemiological studies, reviews and meta-analysis on alcohol consumption and a range of health outcomes. These have contradicted previous studies of the benefits of low-to-moderate consumption of alcohol for reducing all-cause mortality and cardiovascular events [80, 117, 118]. These new studies have shown that while, on the surface, moderate alcohol consumption might reduce the risk of premature mortality, estimates of mortality risk from alcohol are significantly altered by study design and study bias factors [80, 104, 318, 319]. A closer look at studies revealed that the 'abstainer' group included former drinkers and people who did not drink due to other health issues. This creates a bias that made light to moderate drinkers look healthy in comparison. After adjusting for these factors, recent studies revealed

that low-volume alcohol consumption has no net mortality benefit compared with lifetime abstention or occasional drinking [80, 117, 118]. In support of this, important differences were found between non-drinkers and drinkers in this cohort of young adults. For example, non-drinkers had lower levels of physical activity, met fewer dietary guidelines, had poorer CRF, and had a higher prevalence of depression and anxiety. Together, the findings with those of others have implications in terms of the need for greater public awareness of the fact that alcohol consumption may have few benefits for health.

There were significant associations between alcohol, BP and IR that remain important to understand. The findings of this thesis showed that total alcohol consumption was positively associated with BP and inversely associated with IR in a linear manner in a cohort of young adults. These findings were consistent with previous studies in population over a wider age range, older people [146, 147] or even younger people [203]. These findings reflect both potential beneficial and adverse effects of alcohol on health even in younger people. The biological mechanisms underlying the association among alcohol consumption, high BP and IR remain unclear. Possible mechanisms for the effects of alcohol consumption on BP have been proposed including on the central nervous system, sympathetic nervous system, renin-angiotensin system or aldosterone system [213, 214]. Similarly the effects of alcohol consumption on IR may be through beta cell function, hepatic glucose metabolism [234] or growth hormone [235]. Further studies are required to understand the underlying mechanisms by which alcohol can have effects on these risk factors if we are to make sense of the seemingly contradictory literature. It is possible that understanding the physiological and metabolic pathways between alcohol and these outcomes would could harness the positive effects of alcohol on health through interventions. At the very least, such information could be used to better inform the public of the risks of alcohol consumption for health.

8.4.2. Use of a metabolomics platform to understand the relationship between alcohol consumption and cardiovascular or metabolic health

As noted above, the underlying mechanisms for the association between alcohol consumption and cardio-metabolic health remains unclear. While there is mounting evidence that there is no direct association, there is also contradictory evidence of the effects of alcohol on a range of physiological systems. This thesis used information on a quantitative NMR metabolomics platform to identify a diverse range of metabolomics signatures related to alcohol consumption. Metabolomics provides detailed measurements of lipoprotein subclass profiling, FA and small molecules such as amino acids in detail that has not previously been available at

such a low cost on such a large cohort of people. These metabolic markers have recently been linked with the risks of CVD and type 2 diabetes. I propose that this platform could be used to further understand the physiological effects of alcohol on cardiovascular and metabolic outcomes to make sense of the growing body of contradictory findings [244]. Metabolomic platforms have been used to profile people in several population-based epidemiological and genetic studies [242, 244, 320-323]. Some studies have examined alcohol and metabolomics [145] and others have examined metabolomics markers and the risk of cardiovascular events such as myocardial infarction, ischaemic stroke, cardiac revascularization or unstable angina [242] and cardiovascular risk factors [322-324]. Nobody has taken the important step to link alcohol, metabolomics and markers of cardiovascular health in a longitudinal study. Longitudinal studies are needed to confirm the cross-sectional findings reported in this thesis. This could unlock our understanding of the mechanisms at play. It is possible that associations may differ as this cohort ages and there are effects of cumulative alcohol consumption on cardiovascular and metabolic health. These analyses will be possible with future follow-ups of the CDAH study. An understanding of the metabolic pathways underlying associations between risk factors and disease is likely to become increasingly important as we move towards more personalised medicine, including in terms of prevention of disease [325].

8.4.3. Inter-relationship between alcohol and other health behaviours

This thesis focused on the relationship between alcohol consumption and physical activity because these two risk factors contribute substantially to the burden of disease. There was some limited evidence on the potential relationship between alcohol use and physical activity when this research was begun. The association between these two behaviours had not been fully captured across the life course. The findings of this thesis showed that physical activity and CRF were closely correlated with alcohol consumption and played a potentially important role in the relationship between alcohol consumption and cardio-metabolic health. The finding that drinking alcohol is associated with doing less activity over time is important as a potential contributor to weight gain. Alcohol consumption results in consumption of additional ‘hidden’ calories and may slow down metabolism [326]. It is also associated with other issues including dehydration, disruption of sleep patterns, effects on growth hormones that affect muscle gain, and effects on the heart rate [298], which might be compounded by doing less physical activity. The bidirectional nature of the association suggests health promotion activities and public health guidelines should acknowledge the complex association between physical activity and alcohol consumption.

The findings of this thesis provide new longitudinal evidence of the associations between physical activity, sports and alcohol consumption. Childhood physical activity and sport participation were positively associated with adulthood alcohol consumption. These results complement recent findings revealing a positive association between alcohol sports sponsorship and increased drinking among school children [304]. The results of this thesis also support recent findings on the association between membership of community sports clubs for several team (e.g. football and cricket) but not individual sports and higher levels of risky alcohol consumption compared to the general community in Australia [305]. As discussed in the respective chapters, drinking alcohol socially with team mates is perceived to promote team work, social integration, friendships and motivation [306, 307]. As the results showed long term effects, these indirectly support policies to restrict alcohol sponsorship in sports. An important point to consider is the potential cohort effects to my findings. These sports were played among children in the 1980s as the baseline when the social and cultural environments were quite different to those that exist today. However, the recent findings of continued risky drinking in people from sports clubs compared to the general population suggests that the culture may not have shifted as far as we think.

The findings of this thesis that markers of CRF in childhood were associated with a higher risk of AUDs in adulthood were surprising. These findings have implications for our understanding of the associations between alcohol and physical activity against other outcomes. It is likely that previous studies have not captured the complex association between alcohol consumption and physical activity across the life course. The association between fitness and AUDs appears counter-intuitive but is potentially important. This relationship is not believed to be causal but probably reflects social influences linking sport and alcohol consumption (e.g. alcohol culture in sporting clubs). One potential reason for the relationship is that children that did a lot of physical activity and sports continued to do these activities as adults. This exposed them to environments that supported alcohol consumption and, in some people, the development of AUDs. This is, of course, a simplistic view with the development of AUDs complex and likely involving a range of individual psychological, social and biological factors as well as other environmental factors.

Longitudinal studies with follow-up into old ages are required to investigate the relationship of childhood risk factors including physical activity and CRF with alcohol consumption and alcohol use problems in late adulthood. The CDAH study offers opportunities to examine these associations with the completion of its latest follow-up in 2019. It is likely that we will need to use of more complex statistical modelling techniques that can account for time

varying covariates and path analysis to properly understand the complex nature of these behaviours and their effects on health outcomes. We need to understand the longitudinal associations of those behaviours across the life course. This is because inadequate control for the levels of physical activity across the life course in those that consume alcohol may have contributed to the conflicting results regarding the health effects of alcohol. Having a clearer understanding of whether the association between alcohol and health outcomes is causal is important from a public health perspective to ensure that people are given accurate information to manage their own risk.

8.4.4. Changes of alcohol consumption over time

Using the life course perspective to capture how alcohol consumption changes over time, the findings of this thesis showed that there was generally a decline in alcohol consumption from early (26-36 years old) to mid (31-41 years old) adulthood. The findings are supported by a recent publication on patterns in reduction or cessation of drinking alcohol in Australia from 2001 to 2013 that included people's motivation for change [327]. Similarly, a recent national report demonstrated that the proportion of young people abstaining from alcohol has increased, and young people's attitudes, belief and awareness toward minimising alcohol consumption to reduce its related harm might explain for this change [47]. Current Australian alcohol consumption guidelines recommend 'responsible alcohol consumption', which is no more than two standard drinks per day on average, to avoid health risks associated with drinking alcohol [14]. Most people in this cohort were relatively high SES, predominantly Anglo-Saxon cohort were consuming alcohol at or below this level. Recent publications discussed several times in this thesis have shown that "no level of alcohol consumption is safe or improves health" [117, 118]. Together, these data suggest that the public support for alcohol consumption as a regular part of daily life in Australia and worldwide might be changing. It is possible that health promotion messages and alcohol consumption guidelines should be modified to reflect these recent findings. A population-level consumption appears to be decreasing without any significant shift in policies relating to alcohol consumption and it may be a good time to capitalise on public sentiment regarding alcohol consumption. This could include testing policies that have been effective in tobacco control, such as higher taxes or complete bans on advertising.

8.5. Conclusions

This thesis examined alcohol consumption and its relationship with cardiovascular and metabolic risk factors in young to mid-aged adults. There were intriguing associations between alcohol consumption, physical activity and fitness that changed over time that may have implications for understanding the contradictory health effects of alcohol. In general, the findings of this thesis showed that traditional cardiovascular risk factors were not strongly related to alcohol consumption, but that a range of downstream metabolomic signatures did vary according to alcohol consumption. Considering these findings and recent findings internationally, further longitudinal studies of alcohol and health outcomes are warranted.

9 References

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Appendix 8. Published/submitted papers, abstracts and presentations

Two papers have been removed for copyright or proprietary reasons.

They are:
Du, D., Bruno, R., Dwyer, T., Venn, A., Gall, S., 2017. Associations between alcohol consumption and cardio-metabolic risk factors in young adults, European journal of preventive cardiology, 24(18), 1967-1978

and,

Du, D., Bruno, R., Blizzard, T., Venn, A., Dwyer, T., Smith, K. J., Magnussen, C. G., Gall, S., 2019. The metabolomic signatures of alcohol consumption in young adults, European journal of preventive cardiology, published online March 11 2019, https://doi.org/10.1177/2047487319834767

Introduction: There has been recent debate about whether the benefits of alcohol consumption for cardiovascular health have been overstated due to the use of abstainers as the comparator and inadequate control for confounding factors including physical activity and mental health.
Hypothesis: Moderate consumption, but not abstaining or heavy consumption, will be associated with better cardio-metabolic health in young adults.
Methods: Cross-sectional data from the 2004-06 Childhood Determinants of Adult Health study on alcohol consumption from questionnaire and cardio-metabolic risk factors measured in clinics were used. Linear and log binomial regression were used to examine alcohol consumption (categories: none 0g/day; light >0-10g/day [reference]; moderate >10-20g/day; heavy >20-30g/day; very heavy >30g/day) against dichotomous metabolic syndrome (MetS) (NCEP/ATP III definition), continuous MetS risk score, waist circumference, triglycerides, high-density lipoprotein (HDL) cholesterol, blood pressure (BP), glucose, carotid intima-media thickness, and insulin resistance (HOMA-IR). Covariates included socio-demographics, smoking, diet, physical activity, fitness, depression and anxiety.
Results: Of the 2,220 participants (48% males, mean [SD] age 29.5[2.5] years), most had light alcohol consumption (54.2%), less consumed none (13.2%), heavy (5.2%) or very heavy (5.5%) amounts. Only moderate drinking was associated with a reduced MetS prevalence (prevalence ratio 0.64, $p<0.05$) compared with light drinking. Increasing alcohol consumption was associated with higher HDL cholesterol (β 0.05, $p_{trend}<0.001$) and lower HOMA-IR (β -0.08, $p_{trend}<0.001$). Very heavy compared to light consumption was associated with higher systolic (β 3.01 mmHg, $p<0.01$) and diastolic (β 2.07 mmHg, $p<0.05$) BP. Effects were similar when inverse probability weighting was used to account for loss to follow-up.
Conclusion: Moderate alcohol consumption was associated with a lower prevalence of MetS and its components even when compared to light consumption and with account for a range of confounding factors; however, the positive association between very heavy drinking and blood pressure in young adults should not be ignored.

Association between alcohol consumption and cardio-metabolic risk factors in young adults

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Background: There has been controversy regarding the relationship between alcohol consumption and cardiovascular health due to the use of abstainers as the comparator and a focus on old populations. We hypothesised that moderate consumption, but not abstaining or heavy consumption, would be associated with better cardio-metabolic health in young adults. Methods: Cross-sectional data from the 2004-06 Childhood Determinants of Adult Health study on alcohol consumption from questionnaire and cardio-metabolic risk factors measured in clinics were used. Linear and log binomial regression were used to examine alcohol consumption (categories: none 0g/day; light >0-10g/day [reference]; moderate >10-20g/day; heavy >20-30g/day; very heavy >30g/day) against dichotomous metabolic syndrome (MetS) (NCEP/ATP III definition), individual components of MetS, carotid intima-media thickness, and insulin resistance (HOMA-IR). Covariates included socio-demographics, smoking, diet, physical activity, fitness, depression and anxiety. Results: Of the 2,220 participants (48% males, mean [SD] age 29.5[2.5] years), most had light alcohol consumption (54.2%), less consumed none (13.2%), heavy (5.2%) or very heavy (5.5%) amounts. Only moderate drinking was associated with a reduced MetS prevalence (prevalence ratio 0.64, $p<0.05$) compared with light drinking. Increasing alcohol consumption was associated with higher high-density lipoprotein cholesterol (β 0.05, $p_{trend}<0.001$) and lower HOMA-IR (β -0.08, $p_{trend}<0.001$). Very heavy compared to light consumption was associated with higher systolic (β 3.01 mmHg, $p<0.01$) and diastolic (β 2.07 mmHg, $p<0.05$) blood pressure. Conclusion: Moderate alcohol consumption was associated with a lower prevalence of MetS and its components even when compared to light consumption and with account for a range of confounding factors; however, the positive association between heavy drinking and blood pressure in young adults should not be ignored.

(1,978 characters)

Association between alcohol consumption pattern and metabolic syndrome in young adults

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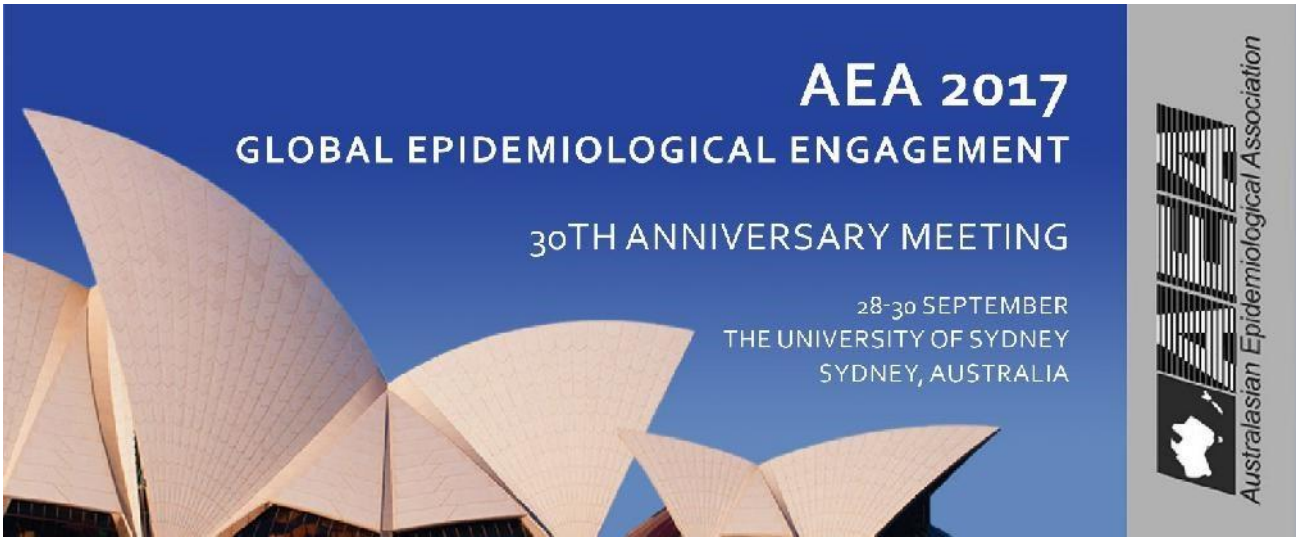
Introduction: There is conflicting evidence regarding associations between types of alcohol consumed and cardio-metabolic health. Combining individual alcohol types into overall patterns of consumption could provide novel insights into these associations.
Methods: We used cross-sectional Australian data collected in 2004-06 from a cohort of 26-36 year olds on alcohol consumption from questionnaire and components of the metabolic syndrome measured in clinics. Latent class analysis classified drinking patterns based on grams consumed per day of beer, wine, and spirits. Multivariable regression was used to examine if drinking patterns were associated with dichotomous (NCEP/ATP III definition) and continuous (from factor analysis of individual components, higher scores indicates worse profile) metabolic syndrome. Covariates included socio-demographics, smoking, diet, physical activity, fitness, depression and anxiety.
Results: Among 2,220 participants (48% males), three patterns of drinking were found: 'moderate beer, wine and spirit' (75.4%, median [IQR] grams/day 6.3 [3.0-10.7]), 'none/light' (13.4%, median [IQR] grams/day 0.1[0-0.5]) and 'moderate wine and heavy beer' (11.2%, median [IQR] grams/day 24.4[17.2-41.3]). 'Moderate beer, wine and spirit' consumers had a non-significantly lower prevalence of dichotomous metabolic syndrome (prevalence ratio [95%CIs] 0.78[0.51-1.19]), but a significantly lower metabolic syndrome score (β [95%CIs] -0.17[-0.26--0.08]) compared to 'none/light' consumers after adjusting for covariates.
Conclusion: The most common pattern of drinking in young adults, moderate amounts of several types of alcohol, was only marginally associated with a better cardio-metabolic health profile. This contrasts with apparent benefits of moderate alcohol consumption for cardio-metabolic health in older people, which may have implications for public health messages.

Keywords: alcohol, risk factors, cardiovascular disease, epidemiology, health-related behaviours, non-communicable diseases

Key Messages:
1. 'Moderate beer, wine and spirit' consumers was the most prevalence drinking pattern in young adults.
2. Moderate amounts of several types of alcohol was only marginally associated with a better cardio-metabolic health profile in young adults.
3. Further research is needed to consider and access the influence of drinking patterns on the alcohol-cardio metabolic health association in young adults, given that apparently contrasts with the findings in older population and might affect the public health messages about alcohol and health.



Parallel Session Abstracts

Alcohol consumption and metabolomics signature in young adults

Mr. Duc Du[1], Prof. Alison Venn[1], Prof. Terry Dwyer[2], Dr. Kylie Smith[1], Dr. Costan Magnussen[1], Dr. Seana Gall[1], A/Prof Raimondo Bruno[3]

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Background: There has been debate regarding the association between alcohol consumption and cardiometabolic diseases. We aimed to investigate the associations between alcohol consumption and a comprehensive systemic metabolite profile in a cohort of young adults with consideration of a range of potential confounders that were not examined in previous studies.

Methods: Cross-sectional data from a cohort of 2,200 participants (age 25-36 years, 52% women) from the 2004-06 Childhood Determinants of Adult Health (CDAH) were used. Alcohol consumption was assessed by questionnaires for each type of beverage (beer, wine and spirits). Circulating lipoprotein lipids, fatty acids and metabolites were measured by a high-throughput nuclear magnetic resonance metabolomics platform. Multivariable linear regression were used to examine total alcohol consumption against 73 selected scaled metabolic measures with adjustment for covariates including socio-demographics, smoking, diet, physical activity, fitness, depression and anxiety.

Results: Higher alcohol consumption was associated with higher concentrations of all HDL subclasses; small LDL particles, and total HDL cholesterol. Higher alcohol consumption was also associated with greater total fatty acids, saturated fatty acids, and monounsaturated fatty acids, but lower concentrations of omega-6 fatty acids. There were also associations between higher alcohol consumption and lower concentrations of glycine, phenylalanine and citrate. Results remained statistically significant ($P < 0.001$) after adjusting for potential covariates.

Conclusions: The results provide an improved understanding of the diverse molecular processes related to alcohol consumption. Metabolic signatures reflecting both alcohol consumption and cardiovascular risk suggest molecular intermediates that may explain the complex relation between alcohol and cardiometabolic diseases.